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THE RELIEF OF PAIN IN CHRONIC (CALCAREOUS) PANCREATITIS BY SYMPATHECTOMY

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CHRONICALLY recurring pancreatitis may cause a wide variety of signs and symptoms but calcareous deposits in the parenchyma of the organ, demonstrable by roentgenograms, and pain are the features common to almost all cases as borne out by the recent reviews (2, 7, 8, 16). The pain which is chiefly in the midline of the upper abdomen may be referred to either or both upper abdominal quadrants and to the back. It is recurring or constant often becoming intolerable and in such cases constitutes the dominant problem in the treatment of the disease. Total or near total pancreatectomy has been recommended and employed by some (Whipple, Clagett (15), Zinninger, Parsons), but the operation is formidable, even unfeasible in some cases. Since relief of pain is the primary purpose of surgical treatment, the interruption of pain pathways from the pancreas may be considered as an alternate and relatively safe means of accomplishing the same end.

In 1945 Mallet-Guy, Jeanjean and Serrettaz performed unilateral subdiaphragmatic splanchnicectomy in 11 patients for relief of pain from chronic pancreatitis. In these patients 10 operations were done on the left side, 1 on the right. Seven had complete relief of pain during follow-up periods varying from 6 to 35 months. Four had one or more attacks of pain after operation. Smithwick reported complete relief of pain 6 months after resection of the right sympathetic chain from the third to the twelfth thoracic and right splanchnicectomy in 1 case. Fontaine, Forster, and Stefanini reported 1 case of "bilateral splanchnicectomy" for "chronic sclerosing pancreatitis" which seemed to have been effective in relieving pain. Reinhoff and Baker in 1 case performed bilateral resection of the sympathetic chains from the twelfth thoracic to the second lumbar, bilateral splanchnicectomy, and bilateral vagotomy with relief of pain and no recurrence after 10 months. Grimson, Hesser, and Kitchin treated 1 patient by removal of both celiac ganglia and of the superior mesenteric ganglion, but the pain returned after 5 months. deTakats and Walter performed a right splanchnicectomy and resection of the right sympathetic chain from the ninth to the twelfth thoracic in 1 patient with relief of pain and no recurrence after 6 months. Ray and Neill, in 1 patient, obtained partial relief of pain after resection of the right greater splanchnic nerve and the ganglionated chain from the seventh thoracic to the third lumbar, but total relief after a similar procedure was performed on the left side.

The diversity of these procedures is confusing and leaves unsettled whether unilateral or bilateral deafferentation is required, whether the vagi may play any role in the transmission of pain impulses from the pancreas and how

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extensively the sympathetic system need be resected for relief of pain. In this report, the case already referred to (11) will be described more fully and 4 additional cases of intractable pancreatic pain (3 cases of calcareous pancreatitis and 1 of pancreatic carcinoma) treated by sympathectomy will be added. Still another type of sympathectomy was employed in the latter cases than any heretofore described and since this might serve only to add to the confusion the available data regarding visceral pain pathways in man will be reviewed in an attempt to arrive at a rational approach to the problem.

CASE REPORTS

CASE 1. C.T. (No. 465637), a 37 year old housewife and mother of 5 children, was admitted to the New York Hospital complaining of pain in the upper abdomen and back beginning 3 years before. At first the pain came in attacks lasting 2 to 4 days at intervals of 3 to 4 weeks, but gradually periods of freedom from pain diminished and for about 6 months pain had been constant. She had been confined to bed and had required daily doses of morphine for several months before admission to the hospital. The pain was described as severe, aching and boring in the epigastrium extending toward the right and left hypochondria and through to the back. Vomiting was frequent and there had been a weight loss of 20 pounds. There was no history of alcoholism and at another hospital an exploratory operation a year before had disclosed a normal gall bladder and common bile duct.

The abdomen was scaphoid, which facilitated the palpation of a moderately enlarged, hard, fairly movable and tender pancreas. Laboratory findings including the following were within normal limits: blood counts, urine, stool, serum protein, albumin-globulin ratio, blood amylase, glucose tolerance, gastric analysis, cholecystogram, and gastrointestinal roentgenograms. The abnormal laboratory findings included: marked deficiency in amylase, lipase, and protease in the duodenal contents and evidence of extensive calcareous deposits throughout the entire pancreas on roentgenogram.

On January 15, 1947 a right sympathectomy was performed which included resection of the ganglionated chain from the seventh thoracic to the third lumbar and of the greater splanchnic nerve from the celiac ganglion to a point above the contribution of the seventh thoracic ramus.

Following operation she was relieved of her spontaneous pain although pressure over the head and body of the pancreas gave rise to moderate pain in the left upper abdomen. Thirteen days later, exploratory celiotomy under local anesthesia was performed, a biopsy of the pancreas taken and studies made on visceral pain sensation. Aside from the pancreatitis no abnormalities were found. Stimulation of the head and body of the pancreas either by pressure or faradic current resulted in pain referred to the upper abdomen always to the left of the midline. This and other studies which have been reported (13) indicate that the pancreas has a bilateral sensory innervation.

The patient returned to her home, began to gain weight and take up her household duties. She was free of pain for 6 weeks after the first operation, then began to experience mild pain in the left upper abdominal quadrant. This gradually increased in intensity but never attained the degree of her original pain and was not attended by nausea and vomiting as before. The pain in the mid-epigastrium, right hypochondrium, and back did not recur.

On May 5, 1947, three and one-half months after right sympathectomy, a left sympathectomy of similar extent was performed for relief of her residual pain. Following this operation her abdominal pain and tenderness were completely eliminated. She gradually resumed normal activity requiring several weeks to accommodate for a moderate grade of postural hypotension. She gained 20 pounds in weight and when last seen in June 1948 had remained asymptomatic.

CASE 2. C.B. (No. 322099), a 47 year old woman (referred by Doctors William H. Lewis, Seward Erdman, and Allen O. Whipple), was admitted to the New York Hospital for the third time in 2 years complaining of abdominal pain. For 2½ years she had been subject to attacks of pain lasting from 1 to 10 days at intervals at first of several months but more recently of only a few weeks at the most. The pain was a severe deep aching sensation felt principally in the midepigastrium but also across the entire abdomen above the umbilicus and in the back at the upper lumbar level; it was accompanied by nausea and vomiting and required frequent doses of morphine for relief. There was a history of chronic alcoholism. In May 1945 and again in November 1946 the abdomen had been explored, each time disclosing normal abdominal viscera except for firm enlargement of the pancreas and several small 1 to 2 centimeter cysts in the head and body of the organ. A biopsy did not show malignancy of the pancreas.

Examination showed evidence of weight loss and a tender, firm palpable mass in the upper abdomen in keeping with a moderate enlargement of the head of the pancreas. The following laboratory findings did not show significant deviation from normal: blood counts, urinalysis, stool, serum protein, albumin-globulin ratio, blood urea nitrogen, blood amylase, glucose tolerance, cholecystogram, and gastrointestinal roentgenograms. However, roentgenograms of the abdomen showed extensive calcareous deposits through the entire pancreas (Fig. 1).

On June 28, 1947, one stage bilateral sympathectomy was performed which included resection of the ganglionated chains from the eleventh thoracic to the first lumbar and of the distal 6 centimeters of the greater splanchnics (preserving the celiac ganglia).

Recovery from operation was prompt and her abdominal pain and tenderness were completely relieved. For the first 6 months she resumed normal activity, gained weight, and with the exception of 1 short episode of low grade fever and nausea 2 months after operation, which may have represented a painless recurrence of pancreatitis, she remained free of symptoms until December 1947. Then she developed persistent fever and a painless mass of gradually increasing size in the epigastrium. Abdominal incision disclosed the presence of an infected pancreatic multiloculated cyst and a fistulous tract has resulted. However, the patient has maintained a fair degree of nutrition and has remained free of pain for over a year.

CASE 3. A.S. (No. 479792), a 43 year old woman, was admitted to the New York Hospital complaining of recurring bilious attacks for 2½ years. The attacks were characterized at first by nausea, vomiting, and pain across the upper abdomen, lasting from several hours to several days and occurring every 4 to 8 weeks. Six months before coming to the hospital she had a particularly severe attack with pain and tenderness across the upper abdomen and pain also across the back at the same level. She had low grade fever, a leucocytosis of 11,000 to 16,000 and signs of fluid in the abdomen. The attack gradually subsided but she was never wholly free of pain thereafter. She lost 12 pounds in weight, became semi-invalid and required opiates for the periods of more severe pain. At no time had she been jaundiced. She had been a moderate alcoholic for many years.

Examination showed evidence of moderate weight loss and tenderness without spasm on palpation across both sides of the upper abdomen. There was no fever. The following laboratory examinations did not show any abnormality: blood counts, urine, stool, serum protein, albumin-globulin ratio, blood amylase, glucose tolerance, cholecystograms, and gastrointestinal roentgenograms. But roentgenograms of the abdomen showed small calcific shadows scattered throughout the head and body of the pancreas.

On December 24, 1947 one stage bilateral sympathectomy was performed which included resection of the ganglionated chains from the eleventh thoracic to the first lumbar and of the distal 6 centimeters of the greater splanchnics (preserving the celiac ganglia). Recovery from operation was prompt and the relief of her former pain and tenderness was immediate.

On January 6, 1948 an exploratory celiotomy was performed. A light anesthesia of nitrous oxide was administered while the abdomen was opened and the pancreas exposed. The margins of the wound were infiltrated with procaine and the patient allowed to waken. Pressure, manipulation, and faradic stimulation of the head and body of the pancreas failed to elicit any pain. The pancreas was diffusely enlarged in moderate degree and unusually firm. The capsule of the gland was tough and incision into the gland for biopsy disclosed grayish, firm fibrotic tissue.

Fig. 1. Roentgenogram in Case 2 showing extensive calcareous deposits in the pancreas outlining the entire organ. Similar deposits were demonstrated by roentgenogram in the other cases of pancreatitis.

Aside from these changes in the pancreas no other abnormalities of the abdominal viscera were observed on exploration. The biopsy of the pancreas showed "pancreatic tissues extensively fibrosed and the parenchyma distorted."

The patient left the hospital 3 weeks after the second operation. She has remained free of pain or digestive complaints, has gained weight and resumed her normal activities. She was last examined in July 1948.

CASE 4. L.B. (No. 498521), a 45 year old male, was admitted to the New York Hospital complaining of recurring attacks of severe epigastric pain of 7 years' duration. The attacks were sudden in onset, frequently associated with nausea and vomiting, and occurred at least once each day. The pain frequently radiated to the back. He had consulted several physicians and had had 2 abdominal operations at one of which a biopsy of the pancreas was taken. The pathologist reported this as definite chronic pancreatitis. At the second operation a subtotal gastric resection was done presumably as a first stage procedure in removal of the pancreas. No ulcer was found.

The patient was a chronic alcoholic and a confirmed morphine addict. He had been eating poorly for several months, had lost a considerable amount of

weight, and had been confined to his room for 3 months prior to admission.

Examination showed a chronically ill man with evidence of moderate weight loss and an extremely poor nutritional state. His mucous membranes were pale and he had 3 to 4 plus edema of the ankles, legs, and sacrum. There was marked tenderness with slight spasm on palpation of the entire upper abdomen, most marked in the midepigastrium. Temperature was normal. Hemoglobin was 5.5 grams, red blood count 3,500,000, serum protein 5.7 grams per cent, albumin-globulin ratio 4.0/1.7; white blood count, urine, blood amylase, thymol turbidity, prothrombin were unremarkable. Gastrointestinal series showed a normally functioning resected stomach. Previous cholecystograms had been unremarkable. A flat plate of the abdomen showed small irregular ring-shaped shadows of calcific density in the region of the pancreas.

On January 20, 1948, after several days of preparation which included multiple transfusions, intravenous protein therapy, and high caloric nasal feedings, a one stage bilateral sympathectomy was performed. This included the ganglionated chains from the eleventh thoracic to the first lumbar and the distal 6 to 7 centimeters of the greater splanchnic nerves. Recovery from the operation was uneventful.

After operation the patient stated he did not experience the former severe pain but he would not tolerate rapid diminution of the amount of his morphine. The abdominal tenderness present before operation completely disappeared. His general condition improved and when discharged 3 weeks after operation his morphine intake had been reduced from the preoperative amount of 30 to 45 milligrams every 2 hours, to 30 milligrams every 8 hours.

When the patient returned for checkup in July 1948, six months after operation, his general appearance and demeanor were greatly improved. His diet was unrestricted and he had gained weight. He was leading an active life, much of it out of doors. He denied having any of his former pain but had not entirely given up morphine saying he still required ¼ grain in the morning "to get started with the day" and another ¼ grain at night to get to sleep.

CASE 5. E.P. (No. 445857), a 27 year old housewife, was admitted to the New York Hospital in the last trimester of pregnancy complaining of jaundice and upper abdominal pain. She was delivered of a living child and 10 days later the abdomen was explored at operation. A carcinoma of the head of the pancreas was found with metastasis to the liver and periductal nodes. A cholecystojejunostomy was performed in the hope of providing some relief from jaundice. She improved enough thereafter to return to her home but was soon readmitted to the hospital because of severe pain in the epigastrium and right upper quadrant which was only partly relieved by frequent doses of morphine.

The patient was jaundiced, emaciated, and very anxious so that it was difficult at times to evaluate her pain. The liver was not palpably enlarged. Temperature and white blood count were normal; stools were acholic, icteric index 90, blood urea nitrogen 10, and serum protein 6.4. Roentgenograms showed no evidence of pulmonary or bony metastases.

On June 10 and 24, 1947, a two stage bilateral sympathectomy was performed which included resection of the ganglionated chains from the eleventh thoracic to the first lumbar and of the distal 8 centimeters of the greater splanchnics (preserving the celiac ganglia).

The upper abdominal pain did not recur during the month she remained in the hospital but she continued to be apprehensive and complained of lower abdominal pains as well as vague generalized pains which required an average of two 75 milligram doses of demerol daily.

This last case illustrates the limitations of sympathectomy for the treatment of pain which may be only partly of visceral origin. Balloon distention studies of the bowel above the rectum showed complete absence of visceral sensation just as occurs after more complete sympathectomy. It may be concluded, therefore, that the patient's residual pain arose from diseased structures having a somatic sensory innervation or that there was solely a psychogenic basis for the pain. Since either or both conditions obtain in the majority of patients with malignant disease of the viscera interruption of visceral pain pathways by sympathectomy in such cases has limited usefulness. The patient described by deTakats and Walter in whom sympathectomy was performed for relief of pain due to pancreatic carcinoma similarly had an unsatisfactory result.

DISCUSSION

In previous studies (11) it has been shown that pain sense in the pancreas and other abdominal viscera is mediated wholly by visceral afferent nerves which accompany the sympathetic nerves and that pain sense in these viscera is eliminated after the usual bilateral thoracolumbar sympathectomy employed for the treatment of vascular hypertension. However, it is likely that a somewhat less extensive sympathectomy is sufficient to produce abdominal visceral analgesia than is required to sympathectomize the splanchnic vasculature. While the exact pathways and segmental arrangement of visceral afferent nerves are not known, the accumulated in-

formation makes it possible to set certain anatomic limits within which afferent nerves from the pancreas, for example, can be expected to pass.

Most nerves supplying the abdominal viscera traverse the celiac plexus, which includes the celiac and mesenteric ganglia. Pathways for connections between the celiac plexus and the paravertebral ganglionated chains include the splanchnic nerves and a plexus about the thoracic aorta. Of the splanchnic nerves by far the most constant in structure and probably the most important from the standpoint of the transmission of afferent impulses is the greater splanchnic on each side. The lesser and least splanchnic nerves have an inconstant anatomic arrangement in man and are represented by a variable number of nerves which connect the celiac plexus to the upper lumbar and lower thoracic portions of the sympathetic chains; they may be conveniently referred to as the lesser splanchnic nerves. In addition to these pathways there may be direct connections between the viscera and the sympathetic chains which do not traverse the celiac plexus. Upon reaching the ganglionated chains, individual visceral pain fibers leave the chains at the same or at higher levels by way of the rami communicantes leading to the posterior (sensory) roots and to the cord.

A schematic diagram (Fig. 2) of the courses that pain fibers from the pancreas may take through the sympathetic system includes several possibilities.

Pathway *A* passes from the pancreas through the celiac plexus to the ipselateral celiac ganglion. From that point it joins the greater splanchnic nerve or any lesser splanchnics through which it reaches the ipselateral ganglionated chain and thence the cord.

Pathway *B* differs from *A* only in that it fails to pass through the celiac ganglion and passes directly from the celiac plexus to the thoracic ganglionated chain via the splanchnics. Such nerve fibers are seen occasionally during surgical operations in this region and while proof is lacking there is a good possibility that some are afferent fibers. Their presence might explain in part the failure of celiac and mesenteric ganglionectomy to relieve pancreatic pain as reported by Grimson.

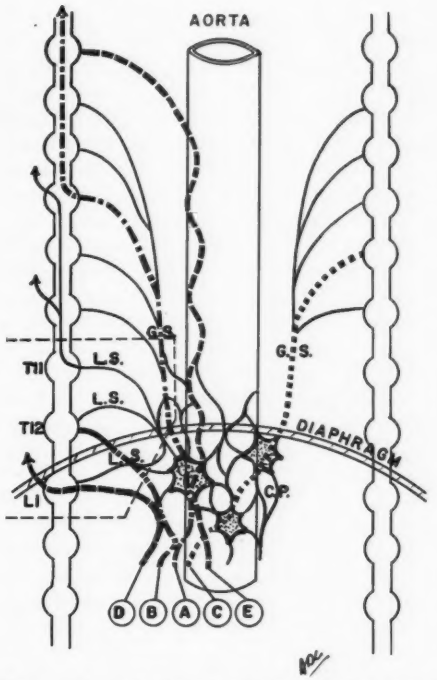

Fig. 2. Schematic diagram of pain pathways from the pancreas. *C.P.*, celiac plexus; *G.S.*, greater splanchnic nerves; *L.S.*, lesser splanchnic nerves. Area within interrupted lines indicates the extent of proposed resection.

Pathway *C* passes through the celiac plexus but joins the contralateral ganglionated chain via the contralateral splanchnic nerves. That such pathways exist and provide a bilateral sensory innervation to the pancreas has been adequately demonstrated in previously reported studies (13).

Pathway *D* passes through nerves that may or may not traverse the celiac plexus but join the lumbar portion of the ganglionated chain and leave the chain at one of the lumbar levels without ascending to the thoracic levels. That such pathways exist has been proved at least for the ureter though not yet established for the pancreas.

Pathway *E* passes through the celiac plexus and ascends with the plexus about the thoracic aorta, leaving the aorta at various levels to join the thoracic ganglionated chain. If such a sensory pathway actually exists it is

likely that connections between the aortic plexus and the ganglionated chain occur through the greater splanchnic nerve though theoretically nerves apart from the splanchnic might connect with the chain in the upper thoracic levels, as indicated in Figure 2, *E*. Since bilateral thoracolumbar sympathectomy from the seventh thoracic to the third lumbar and resection of the greater splanchnic nerves to a point above the contribution of the seventh thoracic rami apparently eliminate sensation in the upper abdominal viscera, separate afferent pathways above the seventh thoracic level either do not exist or are not important in pancreatic pain.

The vagus nerves possess afferent fibers that have been thought by some to be visceral pain fibers though Cannon concluded from animal experimentation that these fibers are part of a visceral reflex arc and not pain fibers. The operation of bilateral sympathectomy and bilateral vagotomy employed for the relief of pancreatic pain by Rienhoff and Baker suggests that they considered the possibility of the transmission of pain impulses via the vagi. The observations of Ray and Neill conclude that abdominal visceral pain sensation is mediated wholly by the sympathetic system. The aggregate observations of Grimson and associates also indicate that the vagus nerves do not play a role in the transmission of abdominal visceral pain.

Thus from these considerations it may be concluded that abdominal visceral analgesia and more particularly analgesia of the pancreas can be achieved by bilateral interruption of all splanchnic nerves. The term splanchnic nerves, however, is a loose one and includes the greater splanchnic nerves and all other nerve fibers connecting the celiac plexus with the lower thoracic and upper lumbar sympathetic chains. The most practical means of accomplishing interruption of the splanchnics is through the operation employed in all but Case 1, namely, bilateral resection of the greater splanchnics and of the sympathetic chains from the eleventh thoracic to the first lumbar.

The operative procedure is as follows: The patient is placed either in prone or lateral position; the latter is preferred. The twelfth rib is resected, the pleura is reflected from the vertebral bodies and the crus of the diaphragm detached. The greater splanchnic nerve is divided at its juncture with the celiac ganglion and freed upward for 8 to 10 centimeters where it is again divided (or avulsed) and the segment removed. The ganglionated chain is then identified and the rami communicantes proximal to the eleventh and twelfth thoracic and the first lumbar ganglia are divided. The chain is divided above the eleventh thoracic and below the first lumbar ganglia and the segment removed. In the process of resecting the greater splanchnic and the ganglionated chain numerous lesser splanchnic nerves connecting them with the celiac plexus or with the pancreas directly will have been divided. The same procedure is carried out on each side and may be done at the same time or in two separate stages. Unless the patient's condition is especially precarious, both sides may safely be done at the same operation.

This operation may not represent the ultimate refinement in producing pancreatic analgesia but it is a relatively limited resection of the sympathetics and should be attended by a minimum of operative risk. With more experience it may be found necessary to remove more of the ganglionated chain for consistent results but it is more likely that less of it will require removal. If additional experience, for example, should show that there are no sensory fibers from the pancreas traversing the lumbar posterior (sensory) nerve roots then it would be unnecessary to resect the first lumbar sympathetic ganglion and the operation could be done entirely above the diaphragm. The operation then would be much like that employed by Peet for the treatment of vascular hypertension. Our experience, however, has shown that division of the attachment of the diaphragm adds no inconvenience and affords better exposure of the upper lumbar portion of the chain, the twelfth thoracic rami and of the lesser splanchnic nerves.

Although it is evident that bilateral sympathectomy is necessary in order to produce analgesia of the pancreas the reports of successful relief of pain by unilateral sympathectomy suggest that in some patients a unilateral operation may be adequate for the indi-

vidual needs. Our experience in Case 1, however, indicated that right-sided sympathectomy cannot be relied upon to relieve all the pain permanently, even though the early result appeared satisfactory, and that for total relief of pain and tenderness in the pancreas a bilateral operation was ultimately necessary. Similarly, a patient (No. 73332, Hospital of the University of Pennsylvania) with chronic calcareous pancreatitis upon whom Dr. J. E. Rhoads performed a right splanchnicectomy and resection of the ganglionated chain from the tenth thoracic to the second lumbar had relief of pain for 1 month only. After left sympathectomy relief of pain was complete. Eckel and Dickinson at the Bronx Veterans Hospital performed a right splanchnicectomy and resection of the ganglionated chain from the seventh thoracic to the second lumbar on a patient with chronic calcareous pancreatitis. Pain relief was partial and transient and left sympathectomy will be done at a later date.

It is difficult to reconcile these reports and our experience with the reports of Mallet-Guy and associates, Smithwick, and deTakats. Each of these has reported lasting and complete relief of pain with unilateral sympathectomy (4 of the 11 patients reported by Mallet-Guy and associates, however, had recurrence of pain). The fact that either right or left deafferentation appears to be equally efficacious in these reports tends to confirm the impression that the pancreas has bilateral sensory innervation and suggests that either unilateral operation is an incomplete deafferentation. It must be concluded, then, that absolute analgesia of the pancreas can be achieved only by bilateral sympathectomy. Partial deafferentation in some patients, however, may be sufficient to give relief of pain.

The question of possible unwelcome effects from bilateral sympathetic resection may aptly be raised for it must be appreciated that any operation in which nerves are cut in order to relieve pain imposes a certain degree of compromise by which one undesirable situation is to be replaced by another which is less undesirable but still acceptable. A sympathectomy of the extent proposed may produce some alteration in blood pressure even in normotensive people but after the initial postoperative period in which symptoms may occur from postural hypotension there should be no notable untoward effects from this source. Also, a sympathectomy to deafferent the pancreas cannot be made selective enough to avoid producing the same effects in other abdominal viscera, chiefly the gastrointestinal tract. Thus, as a result of the operation the visceral pain component of certain abdominal diseases, such as peptic ulcer, cholecystitis, and appendicitis is eliminated. But other symptoms and signs of acute abdominal diseases such as fever, leucocytosis, nausea, vomiting, distention, jaundice, and pain and tenderness from parietal peritoneal irritation (via somatic afferent nerve pathways) would still be present to provide as much warning to the alert physician as exists in some unsympathectomized people with the same diseases. The operation which has been proposed does not affect other gastrointestinal functions or the sexual and reproductive functions of either male or female.

SUMMARY AND CONCLUSIONS

Chronic (calcareous) pancreatitis is often accompanied by pain so intolerable that some surgical measure is necessary for relief. Total or near total pancreatectomy is one method of treatment but it is not always feasible and at best is accompanied by a considerable operative risk and further deprivation of endocrine and enzyme products. The alternative procedure of interruption of the pain pathways from the pancreas is a safer method and the side effects of the operation are not serious.

A review of the several reports of differing procedures for interruption of the pain pathways from the pancreas, together with our own experience in 5 cases of intractable pancreatic pain (4 cases of chronic calcareous pancreatitis and 1 pancreatic carcinoma) has led to the following conclusions:

1. Pain sense from the pancreas is mediated by visceral afferent nerves that traverse the celiac plexus, the splanchnics, and the sympathetic chains on both sides.

2. The vagus nerves play no part in the transmission of pain sense from the pancreas.

3. The principal pathway traversed by pain fibers from the pancreas is via the greater splanchnic nerves, but lesser splanchnic nerves, the lower portion of the thoracic chains, and possibly the upper portion of the lumbar chains may also serve as pathways.

4. The minimal operation thus far found to provide total analgesia of the pancreas and the one proposed as most suitable is bilateral resection of the ganglionated chains from the eleventh thoracic to the first lumbar and of lowest 8 centimeters of the greater splanchnic nerves.

5. Unilateral, right or left, sympathectomy may in some patients provide interruption of enough of the sensory supply to afford relief of pain.

6. While the operation is well suited to the relief of intractable pain of chronic pancreatitis it is of limited value in carcinoma of the pancreas chiefly because of the tendency of the disease to spread outside the organ to pain sensitive areas supplied by somatic sensory nerves.

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BLOOD AND "AVAILABLE FLUID" (THIOCYANATE) VOLUME STUDIES IN SURGICAL PATIENTS

Part I. Normal Patterns of Response of the Blood Volume, Available Fluid, Protein, Chloride, and Hematocrit in the Postoperative Surgical Patient

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THE blood, protein, and crystalloid requirements of the surgical patient are usually estimated on the basis of the history and the values for the hematocrit, protein, and chloride. In states of dehydration, normal values for the laboratory determinations may mask a severe, underlying depletion of the total amount of red cells, protein, or chloride in the body. Conversely, in overhydration and hemodilution with or without the presence of clinically detectable edema, abnormally low values may be found for the concentration of these substances in the blood even though the total amount in the body may be at or close to normal levels. The obvious importance of changes in the size of the blood volume and available fluid in the interpretation of such concentration measurements is not generally appreciated.

The studies in this series represent further efforts to establish the patterns of response of the blood and available fluid volumes in the postoperative patient and in addition to suggest correlations that may exist between such total volume changes and the usual concentration measurements. Through such a program not only will the limitations of the routinely employed laboratory tests be more clearly defined, but in addition their proper interpretation in the assessment of the requirements of the postoperative patient for blood, protein, and crystalloids may be established.

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MATERIAL AND METHODS

Twenty patients, from the ward and private surgical services of the Massachusetts Memorial Hospitals, were subjected to a variety of major general surgical procedures. All patients were considered to be in normal nutritional and fluid balance prior to operation and, except where specifically noted (Table I), received 2000 to 3000 cubic centimeters of 5 per cent glucose in water on the operative day, followed by oral fluids and house diet as tolerated on succeeding days. Blood loss occurring during operation was measured as described in a separate communication (22). Replacement of operative blood loss was withheld in 10 patients. Three to 10 sets of detailed observations were carried out in the preoperative and 10 day postoperative period (Table I).

Plasma volume was determined by a 0.1 per cent solution of Evans blue dye (T1824) according to the method of Gibson and Evans, adapted (10) and modified (11) for use with the Coleman junior spectrophotometer. Dyed samples were corrected for fluid shifts as suggested by Gregerson. Plasma protein concentration was determined by the falling drop method of Barbour and Hamilton. The total blood volume and red cell volume were computed from the hematocrit and plasma volume (13) and the total circulating protein from the plasma volume and plasma protein concentration. Plasma and urine chlorides were determined by the Van Slyke and Hiller modifi-

TABLE I.—RESULTS OF DETAILED STUDIES IN 20 PATIENTS UNDERGOING MAJOR GENERAL SURGICAL PROCEDURES

Case Age Sex	Operation	Days*	Plasma volume c.c.	Red cell volume c.c.	Total blood volume c.c.	Available fluid c.c.	Hematocrit mm. %	Plasma protein concentration gm %	Total circulating protein gms.	Comment
1 45 F	Cholecystectomy and appendectomy	−0	2640	1900	4540	14,400	40.8	6.2	163	
		+1	2680	1840	4520	16,800	40.7	5.8	161	No transfusion
		+2	2970	1800	4770		37.8	6.15	182	
		+3	3090	1840	4850	16,500	36.4	5.9	182	
		+6	2830	1840	4670		39.4	6.4	180	
		+8	2730	1840	4570		40.3	6.4	175	
2 38 M	Cholecystectomy	−0	2640	2320	4960	17,000	46.2	6.9	163	
		+1	2575	2265	4840		46.8	6.4	164	
		+3	2890	2270	5160	20,800	44	6.5		No transfusion
		+7	2610	1900	4510	18,400	42	6.5	170	
		+11	2625	1915	4540	17,850	42.2	6.7	167	
3 35 F	Cholecystectomy	−1	2200	1420	3620	14,400	39.2	7.1	155	
		+2	1880	1220	3100	13,800	39.4	6.9	130	No transfusion
		+7	1880	1200	3080	14,500	39	6.9	137	
		+10	1940	1165	3110	15,000	37.4	6.9	134	
4 38 M	Lumbodorsal splanchnicectomy	−0	3095	2705	5800	22,175	46.6	6.3	195	
		+0	2690	2535	5235		48.5	6.1	165	No transfusion
		+1	2688	2202	4890	26,050	45	6.3	169	
		+6	3650	2240	5890		37.8	6.1	223	
5 66 M	Transurethral prostatectomy	−0	3210	2030	5240	19,200	38.9	5.9	190	
		+0	3040	1980	5020		38.5	6.1	184	Postoperative nausea and vomiting
		+1	3030	1800	4830		38.3	6.2	184	
		+2	3010	1790	4800	18,500	37.3	6.0	182	Received 500 c.c. of blood between (+2) and (+4)
		+4	3160	1990	5150		38.9	5.9	186	
6 64 M	Transurethral prostatectomy	−1	2940	2540	5480	19,000	46.4	6.6	193	
		+1	2760	2200	4960	17,650	44	6.4	177	Unexplained excessive urine volume postoperatively
		+7	2625	1985	4610	18,000	43	6.2	162	
		+11	2890	2080	4970	17,900	41.9	6.5	181	No transfusion
7 48 M	Subtotal gastrectomy	−0	3400	2490	5890	18,700	42.3	5.4	182	Gastric suction inadequately replaced
		+0	2490	2340	4830	17,100	48.5	6.25	156	
		+4	2230	2100	4330	18,700	48.5	6.9	154	
		+8	3020	2070	5090	19,900	40.5	5.9	176	Received 500 c.c. of blood at operation
		+12	2880	1960	4840	19,200	40.5	5.9	172	
8 38 M	Transthoracic vagotomy	−0	2750	2070	4870	21,800	42.8	6.7	185	
		+0	2910	2200	5180		44	6.7	196	
		+1	2380	2200	4580		47.9			Received 500 c.c. of blood at operation
		+4	3300	2200	4530	22,300	39.8	6.45	215	
		+8	3160	1930	5090	22,800	37.8	5.6	180	

TABLE I.—RESULTS OF DETAILED STUDIES IN 20 PATIENTS UNDERGOING MAJOR GENERAL SURGICAL PROCEDURES—Continued

Case Age Sex	Operation	Days*	Plasma volume c.c.	Red cell volume c.c.	Total blood volume c.c.	Available fluid c.c.	Hematocrit mm. %	Plasma protein concentration gm. %	Total circulating protein gms.	Comment
9 40 M	Lumbodorsal splanchnicectomy	−0	3610	2630	6240	19,400	42.1	5.9	212	No transfusion
		+0	3350	2540	5880		43	6.3	212	
		+1	3910	2530	6440	21,800	39.3	5.9	220	
		+3	3980	2260	6240	21,800	36.2	6.2	244	
		+5	4160	2260	6420		35.2	6.1	245	
		+7	3520	2270	5790	18,500	39.2	6.1	216	
		+10	3520	2200	5720	20,800	38.4	5.8	203	
10 43 M	Lumbodorsal splanchnicectomy	−0	3700	3150	6850	25,600	46	7.0	258	No transfusions
		+0	3220	2650	5870		46	6.8	217	
		+1	3650	2650	6300		42.5	6.6	241	
		+3	4050	2650	6500	25,600	39.5	6.7	257	
		+5	4060	2650	6510	34,500	40.7	6.5	264	
		+10	3420	2670	6090	32,200	43.7	7.25	258	
11 42 M	Lumbodorsal splanchnicectomy	−0	3410	2490	5900	18,250	42.3	6.4	218	Received 800 c.c. of red cells suspended in saline between (+3) and (+5)
		+0	3060	2290	5350		42.8	6.9	212	
		+1	3010	1800	4810	17,700	37.5	6.1	184	
		+3	3590	1630	5220	21,500	31.1	6.3	228	
		+5	4090	2560	6600	21,700	38.7	6.4	260	
		+10	3300	2600	5900	21,700	44	6.7	220	
12 40 M	Lumbodorsal splanchnicectomy	−0	3050	2500	5500	16,780	44.5	6.4	195	Received 1500 c.c. of normal saline and 1500 c.c. of 5% glucose in water in first 24 hours following operation No transfusion
		+0	3010	2440	5450		44.8	6.6	196	
		+1	3020	2070	5070	21,200	40.8	6.0	176	
		+3	3080	2010	5070	20,700	39.2	6.1	187	
		+5	2770	2000	4770		41.9	6.7	185	
		+8	2860	1980	4840	19,480	40.9	6.9	197	
13 32 M	Lumbodorsal splanchnicectomy	−0	2675	2150	4825	14,500	44.6	6.2	165	No transfusion
		+1	2825	2065	4890		42.2	5.7	161	
		+3	2955	2055	5010	16,300	40.7	6.1	180	
		+8	2945	1900	4820		39	5.9	173	
14 66 M	Transurethral prostatectomy	−0	3520	1960	5480	19,000	35.7	6.4	227	Received 500 c.c. of blood between (+0) and (+1)
		+0	3530	1860	5390		34.5	6.4	218	
		+1	3810	2000	5810	15,400	34.4	5.6	212	
		+3	3560	1900	5460	26,900	33.6	5.9	210	
		+9	4340	1840	6180	26,900	29.7	6.1	260	
15 54 F	Exploration of knee joint	−0	1795	1405	3200	15,600	43.5	7.4	133	No transfusions
		+1	1965	1335	3300		41.5	7.1	140	
		+5	2215	1315	3530	16,500	37.2	7.0	155	
16 19 M	Mid-thigh amputation	−0	2880	2610	5490	19,300	48	6.8	196	Received 500 c.c. of blood at operation Severe nausea and vomiting for 24 hours postoperatively
		+1	2160	1960	4120	17,200	47.5	6.8	148	
		+10	2060	1750	3753	17,900	45	7.2	148	

TABLE I.—RESULTS OF DETAILED STUDIES IN 20 PATIENTS UNDERGOING MAJOR GENERAL SURGICAL PROCEDURES—Continued

Case Age Sex	Operation	Days*	Plasma volume c.c.	Red cell volume c.c.	Total blood volume c.c.	Available fluid c.c.	Hematocrit mm. %	Plasma protein concentration gm. %	Total circulating protein gms.	Comment
17 50 F	Hysterectomy	−0	2890	1870	4760	19,700	45.2	6.6	190	Received 500 c.c. of blood at operation
		+1	2630	1780	4410	24,400	40.2	6.1	162	
		+5	3150	1800	4950	25,400	36	6.1	194	
		+9	3320	1780	5100	21,200	35	6.0	201	
18 42 M	Herniorrhaphy	−0	2550	1840	4390	15,060	42.1	5.9	151	No transfusions
		+2	2380	1810	4190	16,950	44.3	6.5	154	
		+7	2490	1810	4300		42.1	6.1	152	
19 36 M	Lingulectomy	−0	2610	2185	4795	19,800	45.5	6.8	177	Received 1000 c.c. of blood at operation
		+1	2095	1680	3775		44.5	6.6	138	
		+3	2860	1735	4595	22,400	37.8	6.4	183	
		+6	3320	1720	5040		34.5	7.0	232	
		+10	3630	1890	5520	20,350	34.3	6.6	240	
20 58 M	Exploratory thoracotomy	−0	4230	2140	6370	25,300	33.6	6.5	272	Received 1000 c.c. of whole blood at operation
		+1	3660	2480	6140	27,580	40.2	6.9	251	
		+5	4250	2160	6410	28,400	32.8	6.0	250	
		+9	4440	2090	6500	27,450	32.2	5.9	246	

*Days—(−0)= Preoperative determinations.
(+0)= Determinations within 4 hours postoperatively.
(+1) (+2) (+3) etc. = Determinations on first, second, third, etc. days postoperatively.

cation of the Sendroy method (18). As described elsewhere (11), a 5 per cent solution of sodium thiocyanate was injected intravenously to measure the "available fluid" volume. The thiocyanate ion permeates the plasma and extracellular water, and, in addition, a small amount enters the red cells. In effect it measures the volume of the total extracellular fluid compartment including the plasma volume. In this paper the terms "available fluid," "extracellular fluid," and "thiocyanate space" are used synonomously and refer to the total extracellular compartment of the body water as determined by the thiocyanate method.

RESULTS

Available fluid and chloride concentration. Changes in "available fluid" volume following operation paralleled and were related to the degree of hydration. In 16 cases increases in the available fluid volume of from 16 to 26 per cent were noted by the third postoperative day, representing additions of from 2 to 5 liters of fluid to this compartment (Fig. 1). In 7 cases the "available fluid" was determined within 24 hours following operation and in 6 of these increases in the "available fluid" volumes were observed to have already occurred. Although tending to return slowly toward preoperative values after the fourth day, the "available fluid" compartments generally remained enlarged above preoperative levels for at least 2 weeks following surgery. The greatest increase (26 per cent) in "available fluid" observed in the series occurred in the 1 patient who received normal saline parenterally (Table I, Case 12).

Postoperative decreases in the "thiocyanate space" were noted in 4 of the 20 cases (Fig. 2). Three of these patients were in negative water balance in the early postoperative period (Table I, Cases 5, 6, and 7). In 2, extrarenal water and salt losses through vomiting and gastric suction were unreplaced, and in the third, a 64 year old man subjected to a transurethral prostatic resection, there was an excessive urine volume which equalled the fluid intake. The fourth patient underwent a high

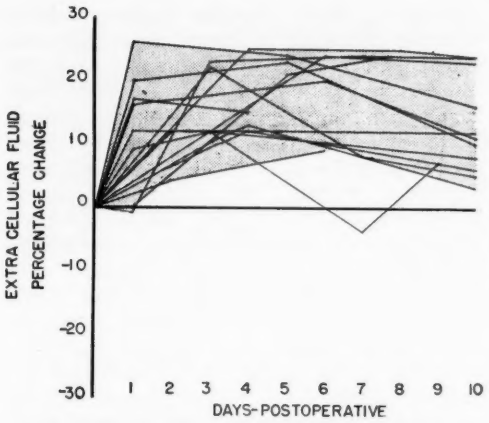

Fig. 1. Illustrates the percentage increases above preoperative (normal) values in extracellular fluid in the postoperative period in 16 of the 20 cases of this series. All 16 cases were in positive fluid balance.

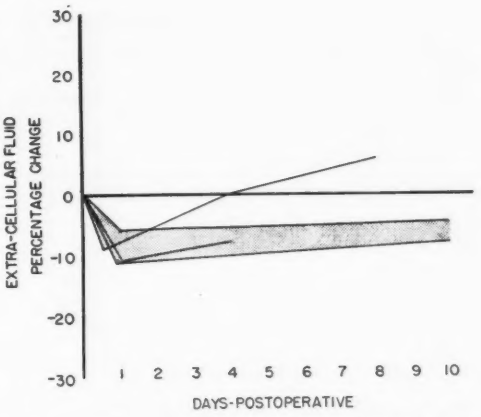

Fig. 2. The percentage decrease in extracellular fluid in 4 cases known to be in negative fluid balance postoperatively. Note consistent decrease as opposed to increase when patient is adequately hydrated, e.g., Figure 1.

thigh amputation which of necessity resulted in the loss of a significant portion of the extracellular space.

Plasma and urine chlorides were determined daily in 5 cases which showed simultaneous postoperative increases in the available fluid volume. All exhibited decreases in the plasma chloride concentrations of from 7 to 12 milliequivalents per liter coincident with the increase in the "available fluid" volume (Fig. 3). Plasma chloride concentration tended to return to preoperative levels about the fifth day. Oral salt intake was not limited save during the period of obligatory intravenous therapy, yet daily total salt outputs in the urine were low, ranging from 1.5 to 3.7 grams on the operative and first 3 postoperative days. Retention of salt also occurred in the 1 patient (Table I, Case 12) who received parenteral saline on the first postoperative day, the intake being 13.5 grams and output 3.36 grams of salt.

In addition to retention of salt, retention of water occurred as indicated by a low urine volume in relation to the fluid intake. The 24 hour urine volumes ranged from 600 to 1000 cubic centimeters during the first 48 hours following operation despite the administration by mouth or parenterally of 3 to 5 liters of fluid during this period.

Therefore, in all cases presumed to be in positive water balance following operation, evidence of fluid retention was manifested by increased "available fluid" volumes, depression of the plasma chloride concentrations,

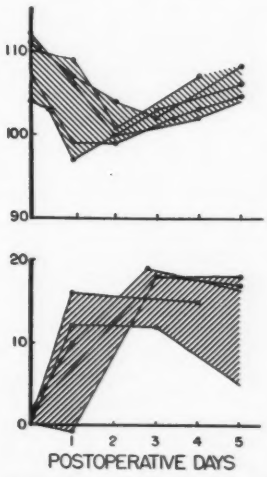

Fig. 3. Illustrates percentage change in available fluid, below, and the decrease in plasma chloride concentration, above, noted in 5 cases following operation and demonstrates decrease in chloride concentration accompanying "available fluid" space increases. Chlorides expressed as milliequivalents per liter and available fluid as per cent change from preoperative (control) value.

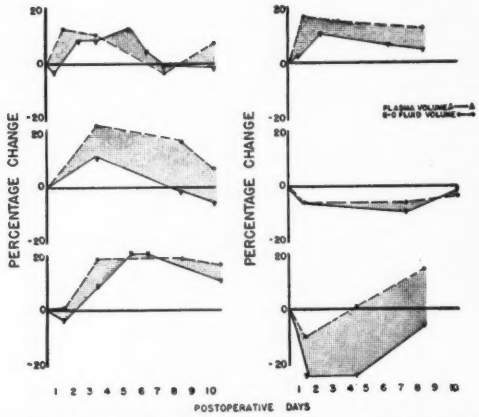

Fig. 4. Illustrates parallel changes in extracellular fluid and plasma volume. Note that plasma volume is below the preoperative level in both instances in which the extracellular fluid was below preoperative values.

and decreased urinary output of water and salt. In cases known to be in negative water balance postoperatively, corroborative evidence of inadequate hydration was afforded by the decreases observed in the "available fluid" volume during this period.

Plasma volume. Plasma volume changes in general tended to reflect the changes in "available fluid" (Fig. 4). In addition the degree of change was closely related to the extent of blood loss. It is noteworthy that following operative blood loss, plasma volume replacement did not take place in any case in the series unless the "available fluid" volume was equal to, or above, the preoperative level.

In the 10 patients who received no operative blood replacement, the pattern of change of plasma volume over the 10 day observation period followed remarkably similar trends. The general pattern of change is demonstrated by the following 2 cases (Figs. 5 and 6). In the first case (Fig. 5), a cholecystectomy had been performed with a blood loss of 150 cubic centimeters. Restoration of plasma volume did not begin until after the fourth postoperative hour, but at the 24th hour, operative plasma losses amounting to 90 cubic centimeters had been replaced. The plasma volume increase continued until the third day, overshooting by 17 per cent at this time and declining toward the preoperative value over the succeeding 7 days. Similar plasma volume changes following a larger uncompensated blood loss of 1080 cubic centimeters are charted in Figure 6. After the fourth hour, and before the 24th hour, the plasma volume increased by 690 cubic centimeters, returning to preoperative levels. Plasma volume continued to increase, the maximum point of overshoot occurring on the third day and finally returned to the preoperative value on the fifth day.

The plasma volume changes in the 10 untransfused, but adequately hydrated, patients are plotted in Figure 7. Four trends can be observed in the 9 cases which exhibited increased "available fluid" volumes: (a) little to no plasma volume replacement occurred within the first 4 postoperative hours, (b) replacement of plasma losses of all magnitudes observed in this study tended to occur by the 24th hour, (c) the maximum point of plasma volume "overshoot" was reached on the third day, and (d) plasma volume decreased after the third day, tending to return to preoperative levels by the 10th and 14th day. By contrast, in the single patient of this group in whom the "available fluid" volume was decreased after operation, the plasma volume remained 6 to 10 per cent below the preoperative level for 7 days, showing no attempt toward restoration to the preoperative level thus illustrating the dependence of the plasma volume on the state of hydration as manifested in the available fluid volume.

Red cell volume. In the adequately hydrated patient, while the replacement of plasma and available fluid volumes following the blood loss associated with surgery was rapid, the red cell volume usually failed to change significantly from the level observed immediately after operation throughout the period during which the extracellular fluid and plasma volumes were increased. However, in several cases in which postoperative blood loss occurred, the red cell volumes exhibited further postoperative decreases, reflecting the extent of blood loss after operation. The significance of uncompensated operative and postoperative depletion of red cell volume following certain types of operative procedures is discussed in another communication (22).

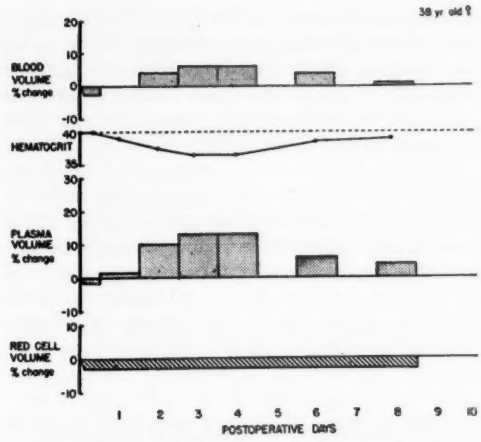

Fig. 5. Illustrates in detail postoperative plasma volume increase after cholecystectomy in patient with blood loss of 150 cubic centimeters. Note concomitant hematocrit decrease and total blood volume increase.

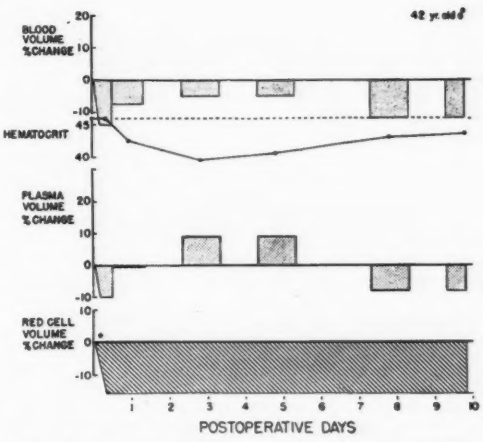

Fig. 6. Plasma volume increase after uncompensated blood loss of 1100 cubic centimeters after 1st stage lumbodorsal splanchnicectomy. Plasma volume overshoot failed to restore total blood volume to preoperative levels.

Total blood volume. Since the red cell volume showed little fluctuation following the period of actual blood loss the total blood volume change closely reflected the fluctuations previously noted in plasma volume. As with plasma volume, blood volume losses tended to remain unreplaced during the first 3 or 4 hours postoperatively. The point of maximum blood volume increase usually occurred on the third post-blood-loss day (Figs. 5, 6), corresponding to the point of maximal plasma volume increase, then gradually receded during the succeeding 7 days as the plasma volume returned toward preoperative levels.

Blood volume responses could be divided into two groups in relation to the amount of blood loss (Fig. 7). Group A with blood losses of less than 400 cubic centimeters exhibited plasma volume "overshoots" adequate to replenish completely both plasma and red cell losses, and to restore blood volume to preoperative levels by the third postoperative day. Group B in which blood loss was in excess of 400 cubic centimeters produced plasma volume increases which were in general greater than those of group A and completely restored the plasma volume losses. However, plasma volume overshoots in group B were insufficient to compensate completely for the excessive red cell loss. In group B, therefore, the total blood volume was not restored to the preoperative values.

Hematocrit. Within the first 3 to 4 hours following operation the hematocrit varied negligibly from preoperative values. Subsequently, it fell steadily for 3 days reflecting the plasma volume increase. Minimum hematocrit values were recorded between 70 and 80 hours following blood loss corresponding with the time of maximum plasma volume increase. With blood losses of less than 200 cubic centimeters the maximum hematocrit fall at 24 hours was 2.4 millimeters per cent and at 72 hours 4.4 millimeters per cent. Where blood loss was from 200 to 500 cubic centimeters, the maximum 24 hour reduction was 3 millimeters per cent and the 72 hour fall 4 millimeters per cent. With uncompensated blood losses of between 500 and 1500 cubic centimeters the hematocrit decrease at the end of 24 hours ranged from 4 to 6 millimeters per cent and at the end of 3 days from 5.5 to 11 millimeters per cent. In general, therefore, in the group in which the blood loss was great the extent of the hematocrit fall at the end of 72 hours was directly related to the amount of blood loss, provided the patient was in positive fluid balance.

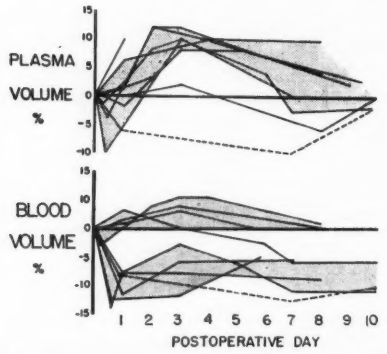

Fig. 7. Illustrates percentage changes in plasma and total blood volume. The two distinct patterns of blood volume response are related to the amount of blood loss. Total blood volume was completely restored by plasma volume overshoots in cases in which blood loss was less than 400 cubic centimeters. With blood loss in excess of 400 cubic centimeters plasma volume overshoots were insufficient to restore total blood volume to preoperative values. Dotted line represents the only patient in this group who was in negative fluid balance and blood volume, plasma volume, and "available fluid" were below preoperative values.

From the third to the tenth days, the hematocrit value tended to rise as plasma volume overshoots were dissipated. However, in no case did the hematocrit return to preoperative levels by the tenth day unless the red cell volume had been restored completely by transfusion.

Circulating protein. Changes in total circulating protein closely paralleled those of plasma volume (Fig. 8). The decreases in total circulating protein within the first four postoperative hours were consistent with the amount of blood loss. Following this period, and within 24 hours, additions of from 5 to 25 grams of protein occurred, usually restoring the total circulating protein to within 3 per cent of the preoperative values. The addition of protein to the plasma most often continued until the third day with overshoots of 5 to 15 per cent, representing daily gains of 12 to 25 grams of protein to the circulation. After the third day the total circulating protein diminished toward normal preoperative levels, continuing to parallel plasma volume changes.

As with the hematocrit, plasma protein concentration varied negligibly from preoperative levels during the first 3 to 4 postoperative hours. However, in contrast to the subsequent increases in total circulating protein, the plasma protein concentration fell 2 to 15 per cent by the 24th hour, reflecting in some degree the simultaneously occurring plasma dilution. This decreased plasma protein concentration was maintained in 15 of the 20 cases during the first 5 postoperative days, and in more than 10 cases throughout the 10 day period of observation. At no time was it possible to judge the amount of the total circulating protein, or recognize increases in total circulating protein above preoperative levels by observation of the plasma protein concentration alone.

DISCUSSION

Data gathered in this study indicate that postoperative changes in the blood, and extracellular fluid volumes as well as in the hematocrit and protein follow a number of well defined patterns. (1) Retention of water and salt in the extracellular compartment tends to occur in the patient in positive fluid balance and is manifested by a decreased urine volume and an increased "available fluid" volume, with dilution of the extracellular salt, and consequent decrease in the plasma chloride concentration. (2) Changes in plasma volume tend to parallel and depend upon changes in the "available fluid." (3) Total circulating protein usually varies with plasma volume. (4) Plasma protein concentration usually decreases and tends to remain low due to plasma dilution even though total circulating protein values rise well above preoperative levels. (5) When uncompensated blood loss has occurred, the hematocrit tends to fall significantly for 3 days and reflects the increase in plasma volume. (6) If adequate hydration is maintained, the hematocrit value in the presence of uncompensated blood loss ordinarily does not return to preoperative levels within the 10 day convalescent period.

Retention of water and salt. The tendency of surgical patients to excrete a small volume of urine despite a large fluid intake in the early postoperative period is a common clinical observation. Detailed fluid balance studies have demonstrated that even the well hydrated surgical patient tends to retain both salt and water after operation (1, 6, 23). Enlargement

of the "available fluid" compartment as measured by thiocyanate has been observed following various types of disease and operation (11, 15, 16, 20). Eighty per cent of the cases in the present study exhibited similar increases in the "available fluid" volume which took place within 24 to 72 hours following surgery. That such increases in "available fluid" volume were most probably dependent on the state of hydration is demonstrated by the 3 cases in the series who were in negative fluid balance following operation and in whom the "available fluid" fell below the preoperative values. Depression of urinary water and salt output was consistently observed in the 5 patients subjected to special chloride studies, confirming the reports of Coller and of Abbott.

Plasma volume. Plasma volume recovery following surgical blood loss occurred in this series only in the 16 patients who were in positive fluid balance and exhibited normal or enlarged "available fluid" compartments. The dependence of plasma volume upon the "available fluid" volume and state of hydration has been noted previously under experimental conditions in dogs by Mellors, Muntwyler, Mautz, and Abbott (17). Furthermore, following acute hemorrhage in dogs, plasma volume replacement is greatest and most rapid in animals given infusions of crystalloids (19). Warren and his co-workers maintained plasma volume and prevented shock in dogs following extensive plasmapheresis by the administration of crystalloid solutions to the point of edema formation, and on this basis have suggested that interstitial fluid pressure, a function of the extracellular fluid volume, is the agent of importance in maintaining or increasing plasma volume under these conditions.

In the present studies the pattern of time relationships of plasma and "available fluid" volume responses suggests that in the adequately hydrated postoperative patient a similar mechanism for the preservation of blood volume may be activated in man. Following a latent period of 3 to 4 hours after operation there began a simultaneous increase in "available fluid" volume and plasma volume (as well as total circulating protein) which uniformly reached a maximum on the third day.

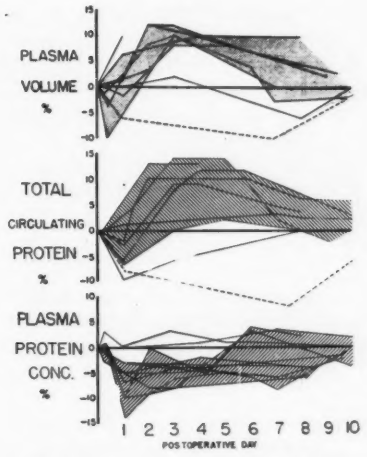

Fig. 8. Illustrates percentage changes in plasma volume, total circulating protein, and plasma protein concentration. Note predominant decrease in plasma protein concentration in spite of increase in total circulating protein accompanying plasma volume increases.

A similar 3 day pattern has been noted following large venesections in both animals (9, 19, 24) and man (8). Rapid recovery of plasma volume and associated circulating protein has been noted following war wounds where blood losses of as much as 2000 cubic centimeters occurred on the battlefield (4). Likewise, Co Tui and associates consistently observed that in man plasma volume appeared to be completely restored between large venesections repeated at weekly intervals.

The remarkable ability of plasma volume to restore itself within 24 hours and then to overshoot after surgical blood loss of from 100 to 1500 cubic centimeters was a consistent observation in this study. It is interesting to note that in the patient who suffered further blood loss on the second postoperative day, the point of maximal increase was delayed for an additional 3 days, suggesting that the 3 day pattern of response may be expected to occur after postoperative as well as operative blood loss.

Plasma protein. In patients who were well nourished and hydrated prior to surgery, plasma protein synthesis and transfer from body stores were more than adequate to replenish all operative plasma protein losses ob-

served in this series. As much as 70 grams of protein were added to the plasma in the first 72 hours after operation. The minimum response observed was usually sufficient to restore the total circulating protein to preoperative levels by the 48th hour.

Despite the postoperative increases in total circulating protein noted in the present study, the plasma protein concentration decreased by from 0.2 to 1.0 gram per cent in three-fourths of the cases studied. Such decreases usually appeared within the first 24 hours following operation, simultaneously with the addition of large amounts of protein and fluid to the circulation, and reflected plasma dilution.

Decreases of as much as 0.5 gram per cent in the plasma protein concentration have been noted following many general surgical procedures (5). These findings confirm parallel observations in dogs subjected to hemorrhage (19, 24) and suggest that plasma protein concentration is an unreliable index of the amount of total circulating protein during the period of recovery from acute blood loss. Abbott (2) has previously suggested the unreliability of the plasma protein concentration as a guide to the nutritional status of the postoperative patient and suggested that the measurement of the total amount of circulating protein may be more reliable. In the present study decreases in plasma protein concentration were a normal occurrence in the adequately hydrated patient following surgery and the plasma protein concentration gave no indication of the relatively large increase in total circulating protein which frequently occurred in the postoperative period.

Hematocrit and red cell volume. In contrast to the rapid synthesis of plasma protein and the remarkable restoration of plasma volume in the adequately hydrated postoperative patient, the replacement by the body of major acute depletions of the red cell volume was severely limited. Though reticulocytosis was repeatedly demonstrated in cases in which blood losses were 500 cubic centimeters or more, none the less restoration of the red cell volume by hematopoiesis was slow and often imperceptible during the 10 day period following such loss. Additional experience (21) has demonstrated that in certain cases where extensive depletion of the red cell volume occurred through either operative or postoperative blood loss, restoration of red cell volume may be incomplete, even 6 to 8 weeks after operation. The recognition of this fact has suggested that since plasma volume and circulating protein most often recover rapidly following operation, attention to, and restoration of, a depleted red cell volume by means of infusions of red cells suspended in saline may be worthy of consideration in specific instances.

A consistent finding in this study, 3 days after an uncompensated operative or postoperative blood loss, has been the fall in hematocrit which usually reflects both a deficit in red cells and an increase in plasma volume. A hematocrit that continues to fall after the third day suggests postoperative blood loss. In the present study, hematocrit decreases of 4 millimeters per cent or more within the first 24 hours, and 6 millimeters per cent or more by the third day could not be accounted for on the basis of increase in the plasma volume alone and indicated uncompensated blood loss in excess of 500 cubic centimeters (22). Furthermore, because of the tendency of plasma volume to decrease after the third postoperative day and to stabilize at its approximate preoperative level by the tenth day, a decreased hematocrit 10 days after surgery, at the time when most patients leave the hospital, is indicative of a depleted red cell volume. In our experience the most reliable simple laboratory test for the recognition of uncompensated red cell loss was a decrease of 5 millimeters per cent or more in the basal hematocrit drawn on the third postoperative day.

SUMMARY

Twenty patients, the subjects of major surgical procedures, were studied preoperatively and throughout an 8 to 10 day period following operation. Definite patterns of response were noted postoperatively in the blood, "available fluid," plasma, and red cell volumes as well as in the plasma protein concentration, hematocrit, and total circulating protein. The influence of the state of hydration and amount of blood loss on the patterns

of response of these volumetric compartments and concentration measurements is described, and the significant interrelationships are discussed.

CONCLUSIONS

1. Following blood loss, the mechanism for the preservation or restoration of the total blood volume appears dependent upon a state of positive fluid balance.

2. With patients in negative fluid balance following operation, recovery of the "available fluid," plasma, and total blood volumes is delayed until a state of positive fluid balance is established.

3. In the absence of excessive extrarenal water and salt loss, a daily ration of 2 to 3 liters of 5 per cent glucose in water under the conditions of this study was adequate to establish positive fluid balance and to insure plasma volume recovery.

4. When depleted through either operative or postoperative blood loss, the red cell volume shows little tendency to recover spontaneously within the first 10 days following operation.

5. In the adequately hydrated patient, serial determinations of the basal hematocrit offer the most useful index of uncompensated blood loss.

6. Postoperative decreases in the plasma protein concentration of from 0.2 to 1.0 gram per hundred cubic centimeters are not necessarily indicative of either inadequate nutrition or a depleted total amount of circulating protein.

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CLINICAL STUDIES OF THE HEPARIN COFACTOR

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THE fact that some surgical patients develop postoperative venous thrombosis whereas others do not remains a challenging problem in spite of the formidable array of facts available concerning the coagulation of blood and the peripheral circulation. There is little doubt that disturbances of the peripheral venous circulation and the coagulation of the blood are the principal factors involved in the pathogenesis of venous thrombi. The coagulability of the blood may be increased theoretically by any means whereby the total production or the rate of production of thrombin is increased. One manner in which the amount of effective thrombin may be increased is by a reduction in the quantity of thrombin inactivating agents in the blood. This study was undertaken to determine whether operative procedures altered the thrombin-inactivating substances of the blood and whether any such alteration could be related to the development of venous thrombosis.

Thirty years ago, Howell (7) demonstrated that heparin itself is not an antithrombin agent in that it did not prevent the conversion of fibrinogen to fibrin in the presence of thrombin. The addition of a cofactor found in plasma or serum, however, rendered the heparin strongly antithrombogenic. These observations were confirmed by Quick (11).

The heparin cofactor is designated throughout this paper as the substance in the circulating blood which develops strong antithrombin capacity when heparin is added to it. The heparin cofactor has been designated by a variety of terms such as thrombin co-inhibitor (2), albumin X (12), proantithrombin (18), and heparin complement (19). Its composition is unknown. It is known, however, to be intimately associated with the blood proteins (7, 11). More specifically, it is most closely associated with the serum albumin. Ziff and Chargaff (19) observed in a study of the heparin cofactor by means of electrophoresis that the fast and middle fractions of the albumin were most active as cofactors. Chargaff, Ziff, and Moore (3) also demonstrated some cofactor activity in some globulin fractions. Crystalline albumin has been found to be completely inactive as a cofactor (5). Howell (6) and Quick (11) found cofactor activity to be present in serum as well as plasma in various experimental animals. Astrup and Darling (2), on the contrary, found no thrombin coinhibitor (heparin cofactor) activity in serum prepared from ox blood by either recalcification of plasma, removal of fibrinogen by the addition of a small amount of thrombin, or by denaturation of fibrinogen by heating to 56 degrees C. for 3 minutes. Quick (11) found that both antithrombin and the heparin cofactor were destroyed at 67 degrees C. and postulated that the two were identical. The addition of heparin according to Quick intensified the activity of the natural antithrombin of the blood.

Seegers and associates (14) demonstrated clearly that heparin acts as a catalyst in inactivating thrombin, and that it does not increase the capacity of plasma for neutralizing thrombin. It merely accelerates the process. If given sufficient time, the cofactor inactivates the same amount of thrombin without the assistance of added heparin.

Reasonably accurate measurements of the antithrombin activity of plasma or serum have been possible only since the purification and standardization of thrombin. Measurements of antithrombin activity are made by determining the amount of thrombin inactivated in a thrombin-plasma or thrombin-serum mixture under standard conditions. Heparin cofactor measurements are determined in a similar fashion except that heparin is added to the plasma or serum prior to the addition of

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TABLE I.—RELATIONSHIP BETWEEN TIME OF INCUBATION OF SERUM AND DESTRUCTION OF HEPARIN COFACTOR

Time of incubation	Heparin cofactor units
None	97.2
10 min. at 56° C.	96.2
30 min. at 56° C.	0

thrombin. Methods for assaying the antithrombin activity of the blood have been devised by Wilson (18), Astrup and Darling (1), Seegers and Smith (13), and Hurn and Mann (9).

The heparin tolerance test (coagulability of the blood after the intravenous injection of 10 mgm. of heparin) described by deTakats (4) and the in vitro test of the coagulability of the blood (17) after varying quantities of heparin are added probably represent in part the quantity of heparin cofactor available in the blood. Other factors such as the amount of thromboplastin and thrombin and the rate of conversion of prothrombin to thrombin may contribute to variations in the results of the tests.

Volkert and Piper (16) found an increase of antithrombin in the blood of patients with multiple pulmonary embolism, but normal values were found in patients with minor or moderate thrombotic disorders. They also observed no change in 21 patients who underwent various surgical procedures and developed no thromboembolic complications. Nielsen found antithrombin activity within normal limits in 6 patients with thrombotic diseases. Hurn, Barker, and Mann (8) performed antithrombin determinations on 57 patients who had evidence of either venous or arterial thrombosis and found an average value approximating that of normal individuals. Of the 57 patients, 18 had values above 120 per cent or below 80 per cent of normal. No mention is made of the interval lapsing between the onset of the thrombosis and the time of the antithrombin assays. Volkert (15) found in a study of rabbits that a coagulative irritant such as a silk suture in the wall of a vein elevated the blood antithrombin whether thrombosis occurred or not.

MATERIALS AND METHOD

Heparin. Various commercial heparin preparations were used, all of which contained 10 milligrams per milliliter. The heparin was kept in a refrigerator and a 1/100 dilution was made each day. One-tenth milliliter containing 0.01 milligram was used for each determination of the heparin cofactor.

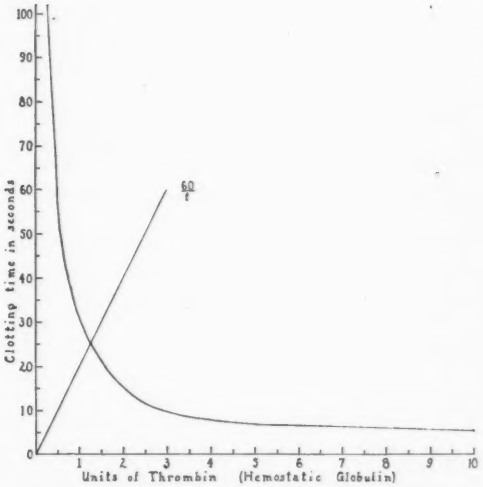

Fig. 1. Relationship between the clotting time in seconds and the concentration of thrombin in units. The clotting time is also expressed as reciprocal minutes $\frac{60}{t}$.

Thrombin. Hemostatic globulin was used undiluted. The thrombin was assayed by comparing its activity to a standard thrombin preparation of known strength.

Fibrinogen. Fraction I was prepared each day so that a 1.65 per cent solution in normal saline was obtained. The fibrinogen was used within 2 hours after being put into solution.

Saline. Normal saline was used to adjust the mixtures to a constant volume.

Serum. Serum was obtained from whole blood drawn during a fasting state. It was inactivated at 56 degrees C. for 10 minutes, 0.1 milliliter of undiluted serum was used for each determination. Contrary to Astrup and Darling's (2) observation that heating of the serum to 56 degrees C. for 3 minutes destroyed the cofactor, we found but slight inactivation when the serum was heated for 10 minutes at 56 degrees C. When heated at this temperature for 30 minutes, however, complete inactivation resulted (Table I). In spite of the fact that a small amount of cofactor activity

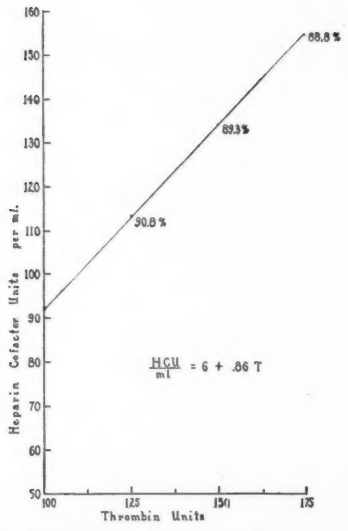

Fig. 2. Relationship between the percentage destruction of thrombin and the amount of thrombin added to the serum.

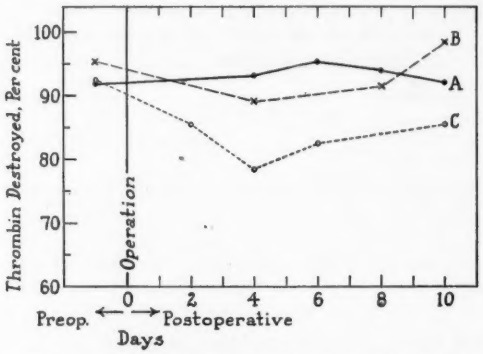

Fig. 3. *A* represents the heparin cofactor activity of a group of surgical patients who developed no thromboembolic complications. *B* and *C* represent the activity of 2 patients who developed venous thrombosis.

was destroyed by incubating the serum for 10 minutes at 56 degrees C., it was considered advisable to continue using this incubation period because of the complete inactivation of any remaining thrombin or prothrombin in the serum.

By using serial dilutions of thrombin, the curve shown in Figure 1 was plotted. The abscissa represents dilutions of thrombin and the ordinate the clotting time in seconds. The thrombin was mixed with 0.8 milliliter of saline and 0.1 milliliter of inactivated serum. One-tenth milliliter of the 1.65 per cent fibrinogen solution was quickly added and a stop watch started. End points were distinct and determined by the first actual flocculation of fibrin. All determinations were done between 24 and 28 degrees C. Variations in the clotting times were found beyond this temperature range. By converting the clotting times in seconds to reciprocal minutes $\frac{60}{t}$, a linear relationship may be established between clotting times and concentrations of thrombin throughout the ascending part of the curve. This relationship is also represented in Figure 1. A linear relationship in this same part of the curve may also be obtained by plotting the logarithms of the clotting times and the concentrations of thrombin. We prefer to read the concentration of thrombin remaining, after inactivation by the heparin cofactor, directly from the curve after noting the clotting time.

It is obvious that significant determinations fall only within clotting times of 10 to 60 seconds. For this reason the amount of thrombin placed in the original mixture is varied in order that the amount remaining may be accurately determined. Figure 2 shows that a linear relationship exists between the amount of thrombin destroyed or heparin cofactor units and the amount of thrombin placed in the serum. This linear relationship does not hold for larger or smaller amounts of thrombin. The equation representing this curve is also shown in Figure 2. By using either the graph or the equation, percentages of normal cofactor activity may be determined and variations from the normal may be compared.

The test is performed as follows: 0.1 milliliter of inactivated serum is added to 0.8 milliliter of normal saline; 0.1 milliliter (0.01 mgm.) of heparin is added and the mixture allowed to incubate for 2 minutes. Ten units of thrombin are then added and incubation is continued for 5 minutes. One-tenth milliliter of a 1.65 per cent fibrinogen solution is quickly added and a stop watch started. The clotting time is determined. The clotting time depends upon the amount of thrombin remaining (Fig. 1) in the mixture and since the amount of thrombin

added is known, the amount destroyed by 0.1 milliliter of serum is easily determined by subtraction. The amount destroyed by 1.0 milliliter of serum is determined by multiplying by 10. A heparin cofactor unit is the quantity necessary to inactivate 1 unit of thrombin. Results may be expressed as either heparin cofactor units or as percentage of thrombin destroyed. Since it is sometimes necessary to use larger quantities of thrombin to obtain significant clotting times, it is preferable to express results as percentage of thrombin destroyed compared to the normal.

Heparin cofactor assays were performed on 67 normal fasting individuals. Destruction of thrombin varied from 83.5 per cent to 97.5 per cent with an average value of 92.0 per cent. Although some variation existed from one individual to another, repeated determinations on the same individual never varied more than 2 per cent. Determinations were completed on 22 patients who underwent major surgical procedures. Tests were performed preoperatively and for the most part every other day postoperatively. Of the 22 patients, 20 developed no thromboembolic complications. They also developed little change in the heparin cofactor activity of their blood. There was an average increase of 3.7 per cent. Three of the patients showed reductions of 0.2 per cent, 0.3 per cent, and 0.4 per cent. The other 2 patients, who developed postoperative venous thrombosis, developed reductions in cofactor activity of 5.8 per cent and 15.0 per cent several days prior to the development of a clinically recognized thrombosis (Fig. 3).

Assays were performed on 6 patients with hypoalbuminemia. Three of the patients had cirrhosis of the liver; 2, pyloric obstruction; and 1, malnutrition. Percentage destruction of thrombin was recorded after several determinations as 80.8, 87.5, 84.5, 82.5, 81.6, and 82.2 with an average value of 83.1 compared to 92 for the control group. In the patient with nutritional hypoproteinemia, as the protein depletion was restored to normal, the heparin cofactor activity rose from 82.5 per cent to 92.5 per cent.

SUMMARY

In this small group of patients the significant observations were that there was very little alteration in the cofactor activity of the serum when no thromboembolic complications occurred. On the other hand, when they did occur, in 2 patients, there were appreciable reductions in the cofactor activity. Whether the latter is cause or effect remains to be demonstrated. It obviously will require a survey of several hundred patients to determine the true significance of these findings.

The observation that hypoalbuminemic patients have a consistently reduced cofactor activity verifies the association of the blood albumin and the thrombin inactivating agents. It also suggests one additional reason for correcting a hypoproteinemic state before surgery.

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CYTOLOGIC DIAGNOSIS OF CANCER OF THE DESCENDING COLON AND RECTUM

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IN recent years exfoliation of neoplastic cells has been noted from many types of malignant epithelial tumors. This method promises to have diagnostic applications particularly for carcinomas arising in internal organs. Although sporadic reports of finding tumor fragments in a variety of body fluids have appeared over a period of many years, it was not until Papanicolaou's work (9) that really serious consideration was given to diagnosis of malignant tumors by cytological examination of human secretions. The vaginal smear technique has had the greatest clinical trial thus far. Diagnosis of cancer of the uterus by means of smears from this site appears most reliable, though the method has been extended to study of secretions arising elsewhere in the body in an attempt to improve early diagnosis of cancer. For example, considerable success has been attained in the diagnosis of lung tumors by examination of either sputum or bronchial aspirations.

Our studies of the past 2 years have centered about the diagnosis of neoplasms in the gastrointestinal tract including stomach, biliary tract, and colon. It is the purpose of this paper to present our experiences with the study of smears taken at proctoscopy and sigmoidoscopy from the large bowel and rectum with special reference to the diagnosis of malignant epithelial tumors.

REVIEW OF LITERATURE

At the time of our preliminary report (12) on the diagnosis of malignant lesions of the rectum and sigmoid colon by cytologic studies of exfoliated cells, we could find only one reference, that of Altgauzen, reporting the use of fresh smears taken at proctoscopy for the diagnosis of malignancy. However, in this report very little definite information was available on the criteria used by him or the results obtained. Since that time Hunter and Richardson have mentioned the use of cell blocks and smears of rectal discharges for this purpose.

The cytologic study of rectal discharges in the diagnosis of diverse diseases of the large bowel is not new, the first reports dating back to the early part of this century. The most practical use of this technique has been in the rapid differentiation between bacillary and amebic dysentery, especially in military service. A number of studies (2, 5, 6) have appeared with special reference to this problem describing the cytology of stained and unstained preparations in considerable detail.

In more recent years Bercovitz (3, 4) has made a study of the cytology of rectal discharges after saline purges in both normal and a variety of abnormal conditions. It was his conclusion that discharges from normal bowel contained few, if any, cells whereas cells of various types and in variable proportions and numbers were present in many pathological conditions. In fact, in one paper (4) he presented a photomicrograph of "degenerating epithelium" from a case of carcinoma in which, as well as could be determined from the illustration, the cells had many of the characteristics seen in those coming directly from malignancies of the large bowel. It is not unlikely that he had observed exfoliated malignant cells without being aware of it.

MATERIALS AND METHODS

Patients selected for the present study included those suspected of having carcinoma, those with diverse gastrointestinal complaints,

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Fig. 1.

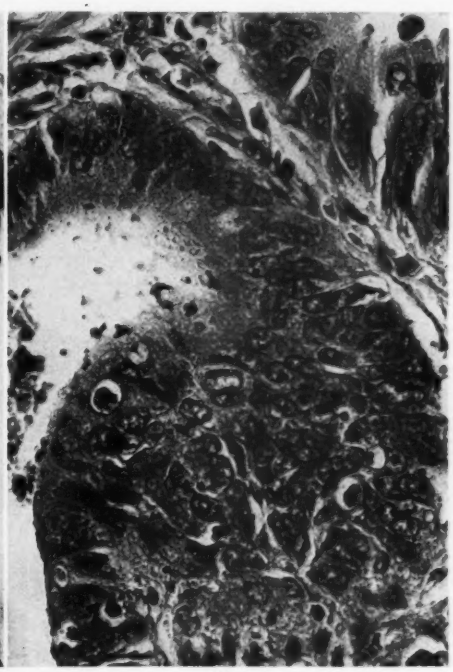

Fig. 4.

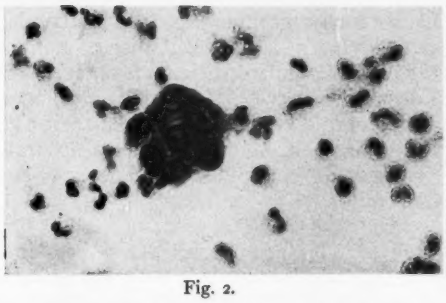

Fig. 2.

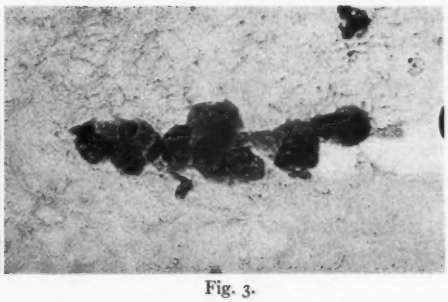

Fig. 3.

Fig. 1. Sheet of normal mucosa. Note regular size, shape, and arrangement of nuclei.

Fig. 2. Smear from patient with ulcerative colitis. Note the large nuclei with dark-staining coarse chromatin. Also note polymorphonuclear cells.

Fig. 3. Exfoliated malignant cells from case of adenocarcinoma of sigmoid. Note variation in size of nuclei and coarse dark-staining chromatin.

Fig. 4. Section of resected specimen from same patient as in Figure 3. Note similarity in type of nuclear structure.

and diagnostic problems. While most of the patients were from the wards of the Massachusetts Memorial Hospitals, a number were derived from neighboring institutions and from the private patients of hospital staff members. All patients received at least one sigmoidoscopy; most, barium enemas; and others, biopsy. In the majority of suspected cases exploration and resection or biopsy were performed giving pathologic confirmation of the diagnosis. Whenever possible, an attempt was made to establish the diagnosis by older conventional methods in addition to the smear technique.

TABLE I.—DISTRIBUTION OF CASES AS TO FINAL DIAGNOSIS

	No. cases
Carcinoma of rectum	8
Carcinoma of rectosigmoid and sigmoid	13
Carcinoma of colon (other)	7
Carcinoma elsewhere in body	11
Ulcerative colitis	5
Functional bowel disturbance	13
Diverticulosis and diverticulitis	11
Amebic colitis	1
Acute gastroenteritis	2
Miscellaneous	39
Total	110

Patients were prepared for sigmoidoscopy with cleansing saline enemas. Material collected on cotton swabs during the examination was smeared onto glass slides immediately and was fixed in chilled acetone before drying had taken place. If the lesion was visible, smears were taken directly from its surface. In those cases in which the lesion was not visible specimens consisted of exudate and mucus clinging to the bowel wall. Bloody mucus seen coming from above the proctoscope tended to be particularly rich in exfoliated cells. Slides thus obtained were stained by the Papanicolaou technique (8). The diagnosis of malignancy was made upon finding groups or clumps of cells whose characteristics will be described in the following.

CYTOLOGY OF THE SMEARS

The types of cells found in rectal discharges and stools, especially in cases of dysentery, have been described in considerable detail (2, 3 4, 5, 6). However, since in the present study the method of sampling differed from those previously described and since the emphasis is placed on the diagnosis of cancer, some discussion of cell types and other structures is warranted.

Smears may contain variable amounts of fecal material depending upon the thoroughness of preparation of the patient for examination. Bacteria, yeast cells, spores, vegetable cells and starch granules, and undigested meat fibers may be encountered. Though such objects are usually quite easily distinguished, on rare occasions a group of cells which are derived from ingested material may cause some confusion.

Mucus is encountered frequently. It is homogeneous in structure, but it may stain in a variable manner depending upon the thickness. Cells may be found imbedded in it.

Squamous epithelial cells are not infrequently found in smears even from the sigmoid to which location they probably are carried on the end of the sigmoidoscope as it is passed from the anus.

Red blood cells are readily recognized (Fig. 8). They may be derived from lesions intrinsic in the bowel, or they may appear as the result of instrumental trauma or vigorous swabbing. Lymphocytes, mononuclear cells, and plasma cells may appear in variable proportions and numbers (Figs. 7 and 8). Polymorphonuclear cells, though not usually seen in normal smears, may be seen in large numbers in some diseases of the large bowel (as ulcerative colitis) (Figs. 2 and 7). Their presence in any numbers is usually significant. Macrophages may be numerous. They are usually large cells containing dark-staining eccentric pyknotic nuclei and may contain vacuoles filled with ingested cells or cell fragments. Karyorrhexis may be prominent with nuclear material represented by numerous small fragments of dark-staining material. Occasionally grouping of the macrophages may occur (5) (Fig. 8). Other mononuclear cells of undetermined origin are not infrequent. Eosinophils have been noted in moderate numbers in several cases, though their significance has not been determined accurately. "Ghost cells" and pyknotic bodies may be observed.

The trophozoites of Endamoeba histolytica were found in considerable numbers in the one case of acute amebic colitis examined by us (Fig. 7). Though the nuclear detail was not as good as is seen in preparations stained with iron hematoxylin, no difficulty was experienced in identifying the parasites in the smears.

The presence of normal or nonmalignant epithelial cells is not unusual. Their number may vary depending upon the friability of the mucosa and the vigor of swabbing (Fig. 1). In general, they are not difficult to distinguish from typically malignant cells. The nuclei are round to oval and quite regular in size

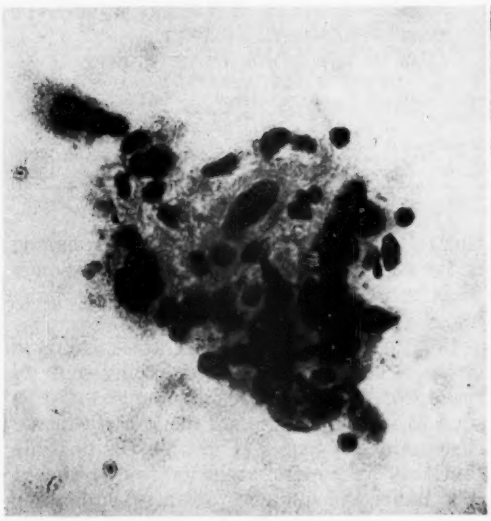

Fig. 5.

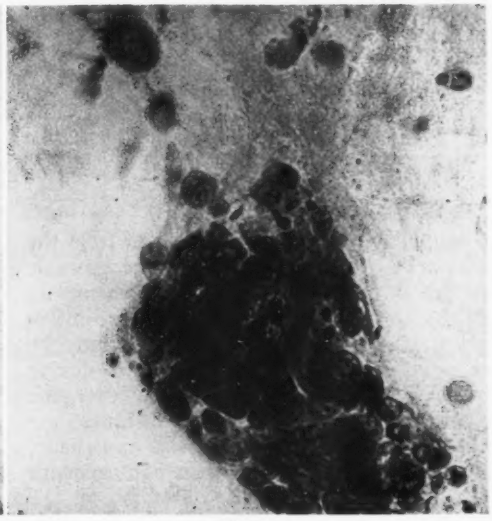

Fig. 6.

Fig. 7.

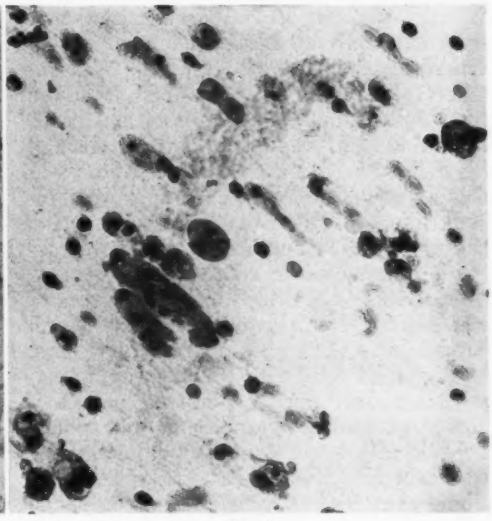

Fig. 8.

Fig. 5. Exfoliated malignant cells in sigmoidoscopic smear from patient with adenocarcinoma of sigmoid. Visualization of the lesion was not possible by sigmoidoscopic examination.

Fig. 6. Exfoliated malignant cells in smear from patient with adenocarcinoma of rectosigmoid.

Fig. 7. Trophozoites of Endamoeba histolytica in smear from patient with amebic colitis, acute. Note polymorphonuclear and mononuclear cells in exudate.

Fig. 8. Smear from patient with "mucus colitis." Note red blood cells (probably due to trauma), macrophages, lymphocytes, plasma cells, and other mononuclear cells.

and staining reaction. There is a well defined nuclear membrane. Chromatin is diffusely scattered throughout in fine granules. There are usually one to three larger dark-staining granules, inconspicuous to moderately prominent. The columnar cells may appear in a

TABLE II.—SMEAR READINGS COMPARED TO FINAL DIAGNOSIS

Positive	Negative	False positive	False negative
9	75	1	12
7	6	Questionable smears*	

*In this column the smears read as questionable are listed under positive or negative with respect to final diagnosis

TABLE III.—RESULTS OF SMEARS ON PROVED CARCINOMAS WITH RESPECT TO THE LOCATION OF THE TUMOR IN THE BOWEL

Location of tumor	Positive	Questionable	Negative
Rectum and rectosigmoid	4	3	2
Sigmoid colon	5	4	3
Other (ascending, transverse, etc.)	0	0	7

palisaded arrangement when viewed from the side, or they may appear in sheets of a mosaic pattern if viewed from above. Occasionally entire glandular crypts are found more or less intact. In these, large goblet cells may be seen with ease. Drying, pressure during smearing, and degeneration may alter the appearance markedly. In such instances the cells and nuclei may vary in size and shape, and the nuclei acquire a pale homogeneous "washed out" appearance.

Anderson noted the effect of osmotic pressure on epithelial cells causing them to assume distorted shapes. He also recognized that large numbers may be desquamated during certain phases of bacillary dysentery. Manson-Bahr (11), in discussing scrapings from the rectal mucosa in the diagnosis of amebiasis, stated that in his experience normal cells had well defined outline and structure whereas in certain pathologic conditions they were indistinct and poorly defined. He also made note of increased numbers of swollen goblet cells in cases of mucus colitis.

Bercovitz (3) described four main types of cells derived from scrapings of the bowel mucosa (obtained at post mortem): (1) large wedge-shaped cells with granular cytoplasm and large oval nuclei composed of heavy rings and containing granules, (2) tall columnar cells with finely granular cytoplasm and large oval nuclei with heavy rings and containing granules, (3) cells irregular in shape with granular cytoplasm and oval to round nuclei having delicate rings which constitute the nuclear membrane with granules included, and (4) square cells with granular cytoplasm and small round solid nuclei. However, in our stained preparations, cytoplasmic granules were not encountered.

X-irradiation seems to alter the appearance of the mucosal cells. In 1 case of rectal stricture following radiation therapy for carcinoma of the cervix, the cells appeared larger, somewhat more basophilic, with heavy staining nuclei.

In 1 case of chronic ulcerative colitis a group of cells were observed having some of the nuclear changes seen in malignant cells such as increased size and moderately heavy chromatin aggregates (Fig. 2). It is possible that they were merely regenerating epithelial cells under the influence of an inflammatory process, such as we have observed in gastric epithelium.

Cells considered to arise from malignancies occurred either singly or in groups. A positive diagnosis was not made if only single suspicious cells were found. Clumps were composed mainly of cells arranged in an irregular fashion. Occasionally the arrangement was fairly orderly; however, in most of these instances cellular morphology was so characteristic that malignancy could be diagnosed. In a number of tumors removed surgically, smears were made directly from the lesion in order to compare known malignant cells with those found in the sigmoidoscopic smears (Figs. 3 and 4).

In general cells exfoliated from tumors of the large bowel showed similar deviations from normal as have been observed in malignant cells arising from tumors in other parts of the body: namely, great variation in size and shape of both the cytoplasm and nucleus with an increase in the nuclear-cytoplasmic ratio. Malignant cells were frequently observed to be considerably larger than normal mucosal cells, while the nuclei were also greatly enlarged in a majority of cases (Figs. 5 and 6). Occasionally giant nuclei were observed, at times with only a small ring of cytoplasm. Binucleate cells occurred in smears from several tumors. Mitotic figures

TABLE IV.—CLINICAL DATA ON PATIENTS WITH SUSPICIOUS SMEARS AND NO PROOF OF CARCINOMA OF BOWEL

Age	Smear diagnosis	Pertinent history	Proctoscopy	Barium enema	Final diagnosis
54	Positive; repeat smear questionable	Adenoca. of cecum resected 4 years before	Mucosa slightly inflamed with a few bleed ng points	Negative	Committed to mental hospital for paranoid psychosis, no evidence of recurrence of tumor
70	Questionable		Granular mucosa at 7.5–17.5 cm. from anus with numerous hemorrhages	Negative	Chronic lymphatic leucemia, with acute polyneuritis
65	Questionable	Hypertrophic and ulcerative proctitis 6 years	Indurated rectal ulcer and leucoplakia	Diverticulosis with narrowing of sigmoid and rectum	Biopsy: leucoplakia, no evidence of malignancy
43	Questionable	Adenoca. of cervix treated with deep x-ray and radium 11 months before	Stricture at 15 cm.	Not done	Curettage: recurrent carcinoma of cervix; rectal stricture presumed secondary to irradiation
40	Questionable		Negative	Negative	Acute and chronic alcoholism
67	Questionable	Epigastric pain 9 weeks with 15 kgm. weight loss	One area of granular mucosa	Negative	Peritoneoscopy with biopsy: metastatic adenocarcinoma to liver, source unknown
62	Repeat smear negative	Sudden onset lower abdominal cramps a few hours before	Negative	Negative	Transient intestinal obstruction secondary to incarcerated hernia

were rare. Two rather distinct types of chromatin arrangement were observed: (1) large to variable nuclei with heavy irregular deposition about the nuclear membrane and large aggregates of chromatin within and (2) large nuclei with diffusely arranged chromatin simulating a fine reticular network. The former was by far the more common. The chromatin tended to take a rather heavy hematoxylin stain. As was expected, gradations between obviously benign and obviously malignant cells were observed. The smears were read as negative, questionable, or positive for malignancy.

RESULTS

The results of this study as it pertains to the diagnosis of cancer of the large bowel are recorded in Tables II and III. In 9 cases of carcinoma the smears were read as definitely positive and in 7 they were read as questionable. Twelve cases of carcinoma were missed. There was 1 false positive result. Six of the questionable smears proved to be from patients without ascertainable large bowel carcinomas although possible sources for abnormal cells were present in most instances (Table IV).

Summarizing these tables it will be noted that in 16 of 28 carcinomas smears were read as positive or questionable; three-fourths of the tumors of the rectum and sigmoid were either correctly diagnosed or suspected on the basis of the smears whereas all the tumors of the ascending and transverse portions of the colon were missed. In 110 cases there was one false positive and three-quarters of all cases were diagnosed correctly. It is of interest to note that both of the tumors of the rectum that were missed completely were reported by the pathologists as early or low grade malignant changes in rectal polyps. This is not unexpected since there is considerable discussion among pathologists as to what constitutes early malignant change in polyps even in tissue sections. There were also 4 cases of obstructive lesions of the colon, 1 in the splenic flexure, 3 in the sigmoid, all of which had negative smears, and which were proved to be inflammatory in nature. Two of these cases were associated with diverticulosis of the sigmoid.

DISCUSSION

Up to this time two principal methods have been available for the diagnosis of malignancy of the large bowel: namely, (1) radiologically by means of the barium enema and double contrast studies and (2) direct visualization through the sigmoidoscope with biopsy. When the latter is possible, there remains little to be desired with the exception that biopsies, especially of polyps, may be unsatisfactory. At times the sigmoid may be difficult to visualize by means of x-ray examination. In one series of cases (10) 9 per cent of the tumors

of the sigmoid were missed by x-ray examination. This is exemplified by 1 of our patients in whom both the initial barium enema and sigmoidoscopy were negative. Smears taken at the sigmoidoscopic examination, however, were read as positive. Subsequent sigmoidoscopy and barium enema both revealed the lesion which was removed surgically and was proved to be an adenocarcinoma of the sigmoid.

In analyzing the results of this study it becomes obvious that the usefulness of this method lies in the diagnosis and confirmation of diagnosis of malignancies of the lower colon: that is, the rectum, sigmoid, and lower descending colon. It should be emphasized that the tumors need not be seen at the time the smears are made, for definite tumor cells were found in 5 cases of carcinoma of the descending and sigmoid colon in which the lesions were not visible. X-ray studies failed to reveal only 1 of these. In 1 case of carcinoma of the rectosigmoid, stricture of the rectum prevented visualization of the tumor by any means, but rectal swabbings repeatedly revealed the presence of many neoplastic cells (Fig. 6).

The accuracy of the methods available for the diagnosis of malignancies of the sigmoid colon and rectum in this series was as follows: (1) sigmoidoscopic examination 67 per cent accurate, (2) x-ray examination 79 per cent accurate, and (3) cytologic study of smears 76 per cent accurate in indicating the possible presence of a cancer. Thus, in at least this small series, the method compares favorably with those already accepted as a means of diagnosis. Also, if the typical malignant cells are present, there is little question as to the nature of the lesion even if it cannot be seen or biopsied in the conventional manner. In short, it extends the effective range of the sigmoidoscope to cover that area of the large bowel in which the greatest proportion of malignant lesions occur (10). From these limited data there is, however, some question as to its usefulness in the detection of early or low grade malignant changes occurring in rectal polyps.

Application of the smear technique to other conditions affecting the large bowel has not been investigated fully by us at this time. However, observations such as large numbers of polymorphonuclear cells in certain phases of ulcerative colitis, their sparsity in mucus colitis, and the identification of Endamoeba histolytica in a case of amebic colitis suggests that routine preparation of smears at the time of sigmoidoscopy may serve as a valuable adjunct to other diagnostic procedures.

SUMMARY

1. A method for the detection of cancer of the large bowel based upon the cytologic recognition of exfoliated malignant cells in smears taken at sigmoidoscopy is described.

2. The cytology of such smears is discussed briefly.

3. The range of usefulness was found to be limited to the rectum, sigmoid colon, and lower descending colon where from two-thirds to three-fourths of the tumors were detected or suspected on the basis of the smears.

4. In this region the smear method compared favorably with x-ray examination and sigmoidoscopy with biopsy.

5. It was possible to detect malignant cells from tumors which could not be seen through the sigmoidoscope.

6. The use of smears in the study of conditions other than malignant is suggested.

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ABDOMINOPERINEAL REMOVAL OF LOW LYING CANCER OF THE RECTUM

Five Year Cures and Local Recurrences

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IN the surgical treatment of low lying carcinoma of the rectum the literature has shown an increasing interest in operations which we consider less radical than the one stage abdominoperineal operation of Miles. In this communication we should like to discuss this problem again from the pathological and anatomical viewpoint as well as from that of the 5 to 10 year cure of the patient.

It seems to us that the principle involved is to determine what surgical procedure gives the patient the best chance for a long term cure and not whether certain operations are technically possible or that continuity of the intestinal tract, however desirable, can be maintained. In the consideration of such a principle, published studies should insist upon *unselected* material, careful pathological consideration of the type of the cancer based on accepted classifications such as those of Broders and Dukes but also on the percentage of involvement of regional lymphatics in cleared specimens, distant metastases, the resectability rate, the operative mortality, and the *five year plus* survival rate. It is only by some such scheme that comparable statistics can be obtained and reasonable conclusions can be drawn.

We have previously reported (2) the 5 to 10 year cures and local recurrences in 167 unselected patients with cancer of the rectum and sigmoid with a resectability of approximately 75 per cent. A careful study was made of the location of the tumor and lymph node involvement (3). One hundred and twelve of these rectal carcinomas were at or below the peritoneal reflection between the anterior wall of the rectum and bladder, and 55 were in the rectum above this junction and in the lower sigmoid.

We have used as a criterion of malignancy of cancer the involvement by cancer of the regional lymph nodes which we consider a most important factor. While the degree of differentiation of the tumor cells (Broders' classification) is generally accepted to be an index of the grade of malignancy, we believe that the degree of invasion and metastasis is a better one and lacks in large part the fallacy of personal judgment in determining grades of histological differentiation of cancer cells. Dukes' classification is also an important means of grading the malignancy of the tumor and stresses the involvement of the regional lymphatics in grade III, the most malignant grade.

A study of our unselected cases is submitted which indicates the grade of malignancy of the tumors as judged by Broders' and Dukes' classification. These figures show that in the Broders' classification grades I and II in general have better prognoses than grades III and IV but that again regional lymph node involvement plays the important role in prog-

TABLE I.—112 EXTRAPERITONEAL RECTAL CARCINOMAS

	Number	Per cent
Alive 5 to 10 years	58	51.8
Postoperative deaths	12	10.7
Lymph node metastases	69	61.9
Of 69 with node metastases, alive 5 years	26	37.5
Of 43 without node metastases, alive 5 years	32	74.4

TABLE II.—112 EXTRAPERITONEAL RECTAL CARCINOMAS

Recurrence	69 with node metastases		43 without node metastases	
	No.	Per cent	No.	Per cent
Local	16	23.2	2	4.6
Liver	11	15.9	2	4.6
Lung, bone, general	3	4.3	1	2.3
	30	43.5	5	11.6

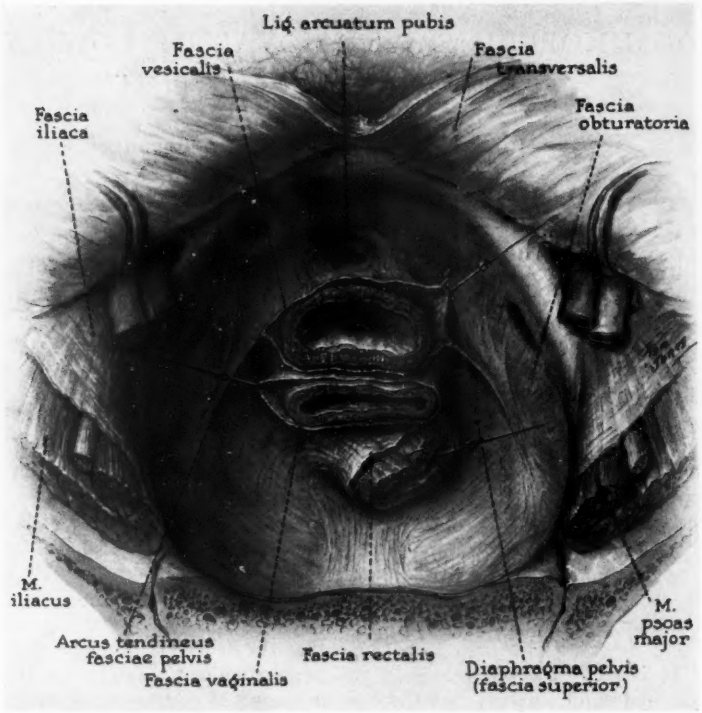

Fig. 1. Anterolaterally, the layers of the abdominal wall have been turned forward along a medial cut; posterolaterally, the alae of the ilium have been cut horizontally, together with the iliopsoas muscles and fasciae; posteriorly, the sacrum has been transected at the same horizontal level. All of the peritoneum and the subserous tissue have been removed to expose the fascia of the pelvis. Within the lesser pelvis, the organs have been transected, together with reflections of the diaphragmatic fascia, the endopelvic fascia. The vesical, vaginal, and rectal tubes of endopelvic fascia have been freed from their respective viscera and retracted. (Courtesy of Arthur H. Curtis, Barry J. Anson, and Chester B. McVay. *Surg. Gyn. Obst.*, 1939, 68: 161–166).

nosis. The Dukes' classification also substantiates this view.[1]

The peritoneal reflection from the anterior wall of the rectum to the bladder was selected as a dividing line in our study because of the regional anatomy of the rectum below this point and because in the experience of a considerable group of surgeons interested in this field of surgery the abdominoperineal operation is regarded as the most radical operation for the removal of the cancer and the tributary lymphatics and therefore the procedure which is most likely to result in a long term cure (4).

The importance of the regional anatomy of the rectum below the peritoneal reflection concerns itself with the fascial and muscular attachments and contiguity of the rectum to the base of the bladder, the seminal vesicles, the prostate, posterior urethra, and vagina in an anterior and lateral plane and to the sacrum and coccyx posteriorly.

This intimate relation of the bowel to these structures allows for early invasion and at-

[1]Duke's classification as modified by Drs. Kirklin, Dockerty and Waugh:
Grade A, Lesion limited to mucosa.
Grade B_1, Lesion extending into muscularis propria but not penetrating it.
Grade B_2, Lesion penetrating through the muscularis propria.
Grade C, Lesion of either B_1 or B_2 with involvement of lymph nodes.

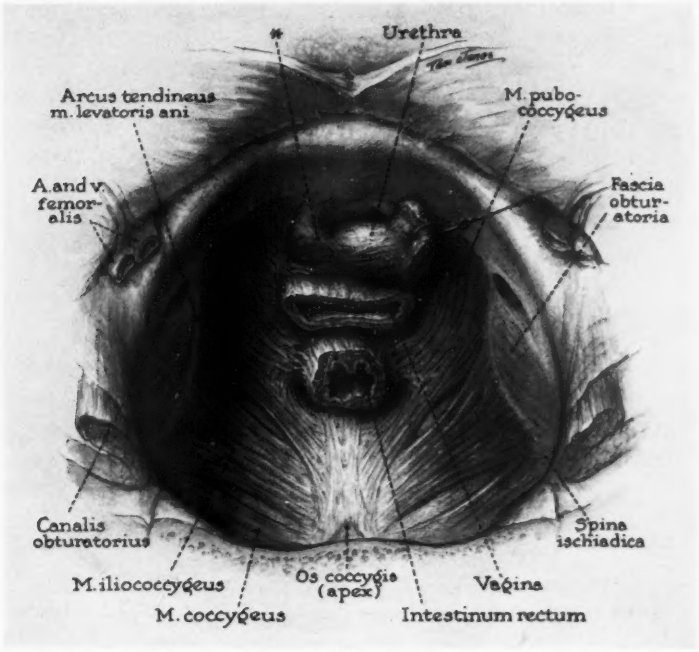

Fig. 2. The fascial layers illustrated in Figure 1 have been removed and the viscera excised to a lower level, in order to demonstrate the muscular constituents of the pelvic floor and the relations of these to the viscera. The urethra has been pulled aside to show the course of the levator fibers on its posterior aspect and the nature of the "pubourethral ligament," indicated by an asterisk. (Courtesy of Arthur H. Curtis, Barry J. Anson, and Chester B. McVay. *Surg. Gyn. Obst.*, 1939, 68: 161–166.)

tachment of cancer of the rectum to structures contiguous to it and for extension through lymphatic pathways where the pectinate line, vagina, prostate, or levator muscles are involved, some of which as the vaginal lymphatics run to the vaginal portion of the base of the bladder or those along the levator muscles to the obturator glands which are difficult or impossible to remove. In this extraperitoneal location of the cancer the encircling bony pelvis makes widespread removal of soft parts around the rectum more difficult than in the case above the peritoneal reflection where there is a well developed mesentery of the bowel containing the lymphatics and where the bowel is freely movable. Not only is it more difficult to perform a radical operation for an intrinsic cancer of the rectum below the peritoneal reflection but the occasional necessity of finding it necessary to remove part of the base of the bladder, seminal vesicles, the posterior portion of the prostate, a section of the posterior urethra, a part of the vagina or some of the presacral fascia indicates a definite risk of local recurrence. At the same time, this radical approach is important because it increased the resectability rate and resulted in more 5 year cures than a more conservative approach (1). Twenty patients with low rectal cancer of the 112 studied had either presacral fascia, a portion of the base of the bladder, a portion of the vagina, urethra or prostate removed because of involvement by the cancer of the rectum. Seven of these lived more than 5 years. Five of the 20 patients had a local recurrence.

A glance at Table I will show that of 112 extraperitoneal cancers of the rectum which

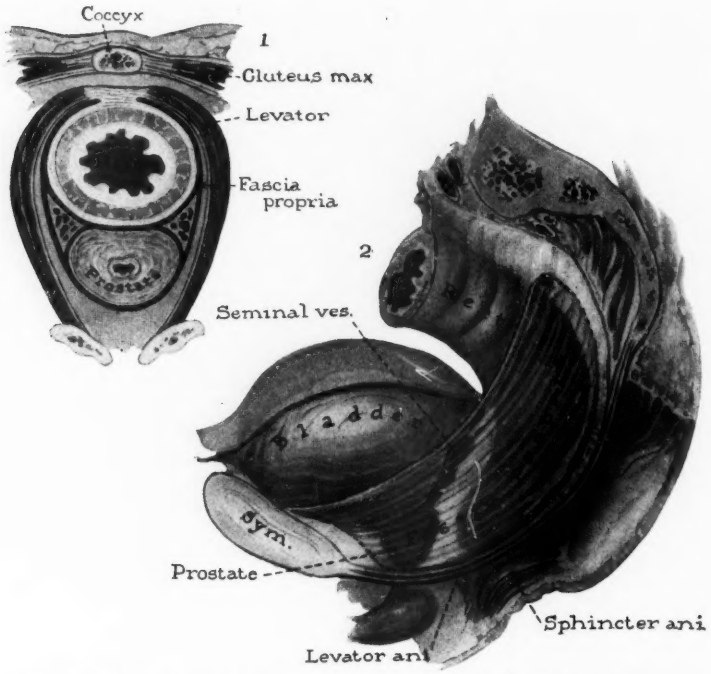

Fig. 3. Relation of fascia propria to rectum and prostate. 1, Schematic cross-section showing continuation of fascia propria around the rectum and prostate. This fascia must be cut to allow separation of the rectum from the prostate. 2, Schematic lateral view of the bowel, showing the origin and extent of the fascia propria indicated by dotted line. (Courtesy W. F. Prior Company. From Chapter VI, Volume 2, Surgery of the Rectum and Anus." by Vernon C. David in Dean Lewis' *Practice of Surgery*.)

were removed by abdominoperineal resection, 51 per cent were alive and free of cancer 5 to 10 years after operation compared to 65 per cent of intraperitoneal cancers of the rectum and lower sigmoid, one-half of which were removed by abdominoperineal resection and one-half by obstruction resection with subsequent establishment of continuity.

Comparing the two groups below and above the peritoneal reflection, about the same number had carcinomatous lymph node involvement (61 per cent and 63 per cent). However, below the peritoneal reflection only 37 per cent with node involvement were alive 5 years or more after operation compared to 51 per cent above the peritoneal reflection.

In the group below the peritoneal reflection *without* node involvement, 74 per cent were alive 5 years or more after operation compared to 90 per cent of the group above the peritoneal reflection.

Local recurrence in the pelvis after operation on cancer of the rectum below the peritoneal reflection with involved nodes was 23 per cent as compared to 3.6 per cent in the group above the peritoneal reflection.

It appears from these facts that cancer of the rectum below the peritoneal reflection treated by abdominoperineal resection has a definitely lower rate of long term cure and a far greater incidence of local recurrence after operation than in cancer of the upper rectum and lower sigmoid treated either by abdominoperineal resection or obstruction resection. It would also appear obvious that any operation on cancer of the rectum which makes a com-

TABLE III.—55 INTRAPERITONEAL RECTAL AND SIGMOID CARCINOMAS

	No.	Per cent
Alive 5 years	36	65.4
Postoperative deaths	4	7.2
Deaths not due to carcinoma	3	5.5
No follow-up	2	3.6
Node metastases	35	63.3
Alive 5 years 18		51.4
No node metastases	20	
Alive 5 years (1, no follow-up; 1, postoperative death) 18		90.0
Obstruction resections	27	
Alive 5 years 18		66.6
Node metastases	16	
Alive 5 years	9	56.2
Postoperative deaths	2	
Short follow-up	1	
No node metastases	11	
Alive 5 years	9	81.9
Postoperative death	1	
No follow-up	1	

TABLE IV.—RECURRENCES IN 55 INTRAPERITONEAL TUMORS

	No. patients	Per cent
Local	2	3.6
Liver	6	10.9
Lung or general	2	3.6
Total	10	18.1

promise with radicability should be avoided. In this connection it is hoped that similar studies of patients treated by other operations which we consider less radical should be published.

A recent article (5) has categorically denied the difference in prognosis after operation in cancer below the peritoneal reflection as compared to cancer above the peritoneal reflection. We suggest some difference in viewpoint. Their conclusions were based on a *selected* group of 137 patients all *graded group II* of Broders' classification. All patients who died during the postoperative period of hospitalization were omitted from their study.

If our figures omitted the patients lost to follow-up, those who died of other causes without recurrent carcinoma and those who died postoperatively (all of which we believe is contrary to sound statistics), 65.2 per cent of the cancers below the peritoneal reflection lived 5 years or more compared to 75 per cent above the peritoneal reflection. Of those having regional involvement of lymph nodes, their method would give us a 5 year survival

TABLE V.—COMPARISON OF 5 TO 10 YEAR SURVIVAL RATE IN CASES OF CARCINOMA ABOVE AND BELOW THE PERITONEAL REFLECTION ACCORDING TO GRADE

Broders' type	Lesions above the level of the peritoneal reflection			Lesions below the level of the peritoneal reflection		
	Patients studied No.	Lived 5 or more years post-operatively No.	Per cent	Patients studied No.	Lived 5 or more years post-operatively No.	Per cent
I	4	4	100.0	6	6	100.0
II	40	25	62.5	62	40	64.5
III	10	6	60.0	41	11	26.8
IV	1	1	100.0	3	1	33.3
	55	36	65.4	112	58	51.8

TABLE VI.—COMPARISON OF 5 TO 10 YEAR SURVIVAL RATE IN CASES OF CARCINOMA ABOVE AND BELOW THE PERITONEAL REFLECTION ACCORDING TO GRADE

Dukes' grade	Lesions above the level of the peritoneal reflection			Lesions below the level of the peritoneal reflection		
	Patients studied No.	Lived 5 or more years post-operatively No.	Per cent	Patients studied No.	Lived 5 or more years post-operatively No.	Per cent
A	3	3	100.0	5	3	60.0
B1	1	1	100.0	5	5	100.0
B2	16	14	87.5	33	24	75.6
C	35	18	51.4	69	26	37.5
	55	36	65.4	112	58	51.8

rate of 49.1 per cent below the peritoneum compared to 60 per cent above it.

In their study (5), all cases were omitted involving the pectinate line as well as those in whom the surgeon felt that the operation might be a palliative one. Study of regional lymph node involvement was made largely on fixed specimens by making numerous cross sections, and the percentage of node involvement by this method gave an incidence of 35 per cent below the peritoneal reflection and of 53 per cent above it. This compares with 61 per cent and 63 per cent in our group. While importance of the resectability rate was stressed, it was not given. The importance of the height of the cancer above the anal region was stressed and the choice of the peritoneal reflection as a landmark was depreciated.

In this connection, we would suggest that the *anatomical position* of a cancer 8 centimeters above the anal margin would vary considerably in a patient 5 feet tall as compared to one 6 feet 3 inches tall but that the peritoneal reflection would be in a relatively fixed position in relation to the regional anatomy below it.

We hold no particular brief for the peritoneal reflection as an arbitrary dividing line in studying results in surgery of cancer of the rectum except that we would stress the importance of the regional anatomy in the surgical treatment and in the long term cure of cancer below the peritoneal reflection. In that portion of the bowel the fascial and muscle attachments as well as contiguity to neighboring structures and the varying pathways of lymphatic spread make complete eradication of the cancer less certain than in high lying tumors of the rectum. By the same token, we believe that less radical surgery than the Miles operation for cancer of the rectum below the peritoneal reflection should be regarded critically until acceptable evidence is published to show that the results of less radical surgery compare favorably with the results of abdominoperineal resection.

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THE DIAGNOSIS AND REPAIR OF PSEUDARTHROSIS OF THE SPINE

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THE operation of spinal fusion for any purpose is followed in some cases by the development of pseudarthrosis, or fusion failure (1,2,3,4,6). This fact is not always recognized in evaluating the end-results of this operation. The fusion operation by whatever technique employed can be expected to achieve the desired therapeutic effect only if it results in solid bone fusion of properly designated spinal segments. Failure to secure fusion then can only mean failure to secure the therapeutic result desired. It is therefore important that we recognize as early as possible in the postoperative course the development of fusion failure so that it may be corrected.

In reviewing all cases of spinal fusion performed at the New York Orthopaedic Dispensary and Hospital during the 10 year period of 1936 through 1945, certain features contributing to the diagnosis of pseudarthrosis are evident and should be emphasized. The original fusion procedures followed the Hibb's technique.

DIAGNOSIS OF PSEUDARTHROSIS

The diagnosis of pseudarthrosis can be made only when the surgeon is aware that the problem of pseudarthrosis does exist and is to be ruled out in each case following operation. The staff at this hospital has realized this problem for many years and has assumed in each case that fusion has failed until proof to the contrary is shown.

Essentially, pseudarthrosis of the spine produces the same symptoms and physical findings as pseudarthrosis elsewhere in the body. However, those as related to the spine are frequently more difficult to elicit. In addition, these findings may frequently be similar to those first presented by the patient preceding spinal fusion.

From the New York Orthopaedic Dispensary and Hospital.

The effectiveness of the operation of spinal fusion in the treatment of any of the clinical conditions in which it has been used cannot be stated until we are certain that the procedure really has resulted in fusion of the spine. Sometimes it may be impossible to answer this question until the fusion area has been exposed surgically and direct examination of the bone mass performed. Usually, however, by careful attention to the postoperative history, physical findings, and roentgenographic examination, a close estimate of the state of fusion may be arrived at prior to resorting to such exploration.

1. Local pain and tenderness. Pain and tenderness sharply localized over any fusion area suggest pseudarthrosis. A patient with lumbosacral strain and instability may present these findings preoperatively and we are aware that a successful spinal fusion does not result in relief of symptoms in all such cases even though they have been carefully selected for this operation. However, the patient that continues with low back pain and solid fusion does not show the sharp localization of pain and tenderness over the fusion plate, demonstrable in pseudarthrosis. Tenderness is best demonstrated with the patient in the prone position, completely relaxed. On deep pressure with the thumb, a limited area is found over the fusion plate that is quite tender, with no radiation of pain from this point. Pressure elsewhere along the spine may show minor degrees of tenderness but on returning repeatedly to the involved area, exquisite tenderness is again elicited, at the same point on each occasion.

Local pain and tenderness are commonly found preoperatively in patients with tuberculosis of the spine. At this hospital these patients are maintained postoperatively at complete bed rest until evidence of arrest of the disease is obtained. This arrest of disease is

a b c

Fig. 1. a, Tuberculosis of the spine involving the first and second lumbar vertebrae. Spinal fusion, eleventh dorsal to fourth lumbar performed on May 22, 1942. b, Further bone destruction and deformity with pseudarthrosis at level of first to second lumbar. Pseudarthrosis repaired on April 28, 1943. c, Further bone destruction and deformity with pseudarthrosis still apparent. Although the defect is quite visible in the fusion plate, this may not always be demonstrable. If it were not, the presence of a pseudarthrosis would still be indicated by the progressive deformity.

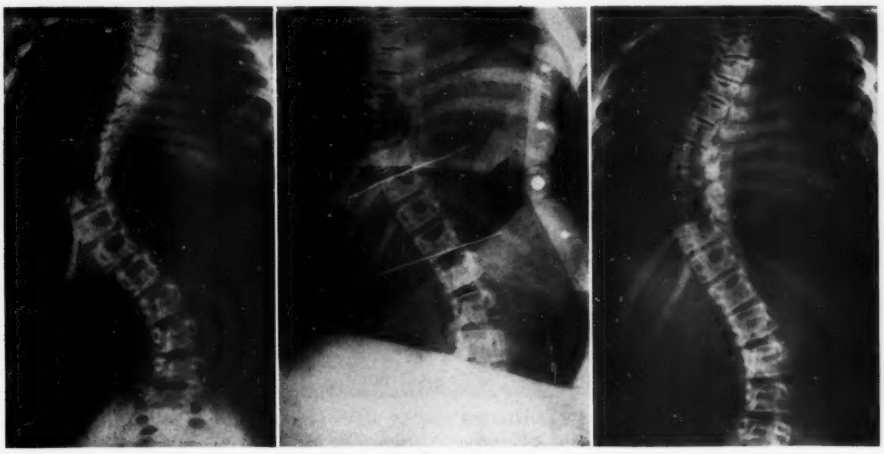
determined by clinical and roentgenographic examination and by the return of the blood erythrocyte sedimentation rate to normal. Should the patient at any time preceding or following ambulation develop localized pain in the area of fusion and should local tenderness be demonstrable, pseudarthrosis is suggested, and further study to determine the presence of such is indicated.

Pain and tenderness are especially helpful findings toward the diagnosis of pseudarthrosis following fusion for scoliosis. They are uncommonly present preoperatively and when found after ambulation with all support removed are indicative of fusion failure.

2. *Progression of deformity or disease.* Surgical fusion of the spine means that the spine is fixed by a continuous column of bone that allows no motion in any plane of the body throughout the vertebral segments involved. Collapse of vertebral bodies and further anterior angulation in tuberculous disease of the spine is not consistent with solid fusion. It is recognized that angulation may take place before the fusion matures, and in such a case progression of deformity may be noted for some time following operation. However, continued and progressing deformity over a prolonged period of time means failure of fusion. Such evidence of delayed or faulty fusion is especially useful in areas of the spine where the fusion mass itself is difficult to visualize roentgenographically. On the lateral films evidence of further destruction and collapse of the vertebral bodies may be demonstrable, a factor indicating failure of fusion (Fig. 1).

Development or progression of paralysis in the lower extremities may also indicate the presence of pseudarthrosis following fusion for tuberculosis, and should always be considered as a possible cause of such, as well as cord compression by tuberculous granulations or abscess uncomplicated by pseudarthrosis. The pseudarthrosis permits continued activity of the disease and so indirectly may contribute to the development of neurological changes in the extremities. Of the 21 patients who developed pseudarthrosis following fusion for tuberculosis during the period of this study, progression of spasticity was prominent in 5, and in them was considered the main clinical feature warranting exploration.

Following spinal fusion for scoliosis, progression of the lateral deformity indicates failure of fusion. Some error must be allowed for placement of the patient for roentgenography and for measurement of the curve. After final removal of plaster jacket any increase in curvature beyond 5 degrees should be regarded suspiciously and failure of fusion should be considered (Fig. 2). This loss of correction is even more significant if it can be shown to have occurred at a single intervertebral level



a b c

Fig. 2. a, Scoliosis. Original curve from the fifth dorsal to second lumbar measured 64 degrees. b, Corrected to 32 degrees and fused. c, Loss of correction to 43 degrees noted at 9 months postoperative. No definite defect apparent by x-ray examination. Because of loss of correction and localized tenderness, fusion plate explored and pseudarthrosis found at level of seventh to eighth dorsal vertebrae.

and not throughout the length of the fusion mass.

3. Roentgen examination. The usual roentgenographic examination of any fusion area, including oblique as well as anteroposterior and lateral views, may or may not show a pseudarthrosis when such is present. When it is demonstrable it is seen as an irregular line of translucency extending across the fusion plate in one or all films. The immediately adjacent bone mass may show an increase in density. Such a line of fibrous union may extend completely across an interlaminal space with solid bone fusion present across one or both articular facets. This latter may be difficult to demonstrate roentgenographically. In such a case the roentgen examination will indicate failure of fusion while actually fusion is solid. Quite frequently the line of fusion failure will extend across the plate in an oblique direction in both the coronal and sagittal planes with solid bone mass overlapping above and below as well as in front and behind. Such a line cannot be clearly demonstrated by roentgenographic examination, so that the usual views which are taken in this situation mean nothing in determining the presence or absence of pseudarthrosis.

At this hospital in cases of suspected fusion failure roentgenograms are taken in the lateral position with the spine placed first in maximum extension and then in maximum flexion. Such technique has been especially useful in the study of fusion in the lumbosacral spine. When the films are superimposed over a strong light, variation in the height of the intervertebral disc space at the level of the pseudarthrosis is demonstrable, together with variation in the alignment of the anterior borders of the vertebral bodies (Fig. 3). In addition, in the flexed position, separation of the fusion plate at the level of the pseudarthrosis may be demonstrable.

4. Exploration. In certain cases the diagnosis of pseudarthrosis cannot be made definitely until the fusion area is exposed surgically. It is our feeling that when doubt as to the diagnosis exists and the clinical picture warrants, exploration is indicated. Adoption of such an attitude will mean that some patients will be subjected to exploration that reveals solid fusion. However, a greater number of patients will benefit from such an exploration.

At exploration the fusion mass is exposed through the line of the old incision. If any

a b c

Fig. 3. a, Roentgenograms taken a year following spinal fusion of fourth lumbar to sacrum. These suggest fusion failure at fourth to fifth lumbar level. b, and c, Lateral views, taken in flexed and extended positions show failure at both the fourth to fifth lumbar level and the fifth lumbar to sacrum level. Note the differences in height of the disc spaces. Also note difference in alignment of anterior borders of bodies of fourth and fifth lumbar vertebrae and sacrum.

doubt as to the location or the number of defects exists, the entire plate should be explored. The area is carefully exposed subperiosteally. If the defect is wide with interposition of considerable fibrous tissue, the stripping will proceed with difficulty across it. This may not be demonstrable if the defect is narrow. If the defect is quite narrow considerable search may be required before it can be demonstrated. The surface of the plate is frequently quite irregular and each indentation must be thoroughly cleaned of fibrous tissue. The defect is then demonstrable as a thin line of fibrous tissue, with the adjacent superior and inferior borders of bone mass moving slightly with respiration or on pressure with some blunt instrument. Movement even though barely perceptible is always demonstrable and failure to demonstrate this means that solid union is present.

REPAIR OF PSEUDARTHROSIS

The defect in the fusion plate is carefully exposed as described previously. The line is followed across the width of the plate, and laterally it will be found to extend into the apophyseal joints. The joint spaces are carefully explored and any remnants of articular cartilage not removed at the primary operation are excised with the fibrous tissue present. If the defect in fusion is wide with free motion across it, the fibrous tissue filling it is excised to a depth of ⅛ or ¼ inch, entirely across the plate. As in the primary fusion, care must always be taken to protect the underlying dura and cord. If the defect is narrow with little motion across it, the surgeon may prefer to limit this excision of interposing fibrous tissue as some degree of fixation is lost through the wide removal of such. At both sides of the midline, narrow troughs, measuring ¼ inch in width and ¼ inch in depth are gouged. These are extended across the defect well above and below into healthy bleeding bone. The troughs are then filled with cancellous bone chips obtained either from the fusion mass itself or from the ilium. Chips are also wedged into the joint spaces after these have been thoroughly cleansed of fibrous tissue or cartilage. Over an area extending across the entire width of the fusion mass and several inches above and below the defect, bone chips with their bases undetached are reflected. These are fashioned in the caudad mass with their bases attached caudally and in the cephalad mass with their bases attached cephalad. Healthy bleeding cancellous bone is thus exposed underneath. Multiple small free bone transplants are then placed in longitudinal fashion to bridge the line of pseudarthrosis with both ends of each

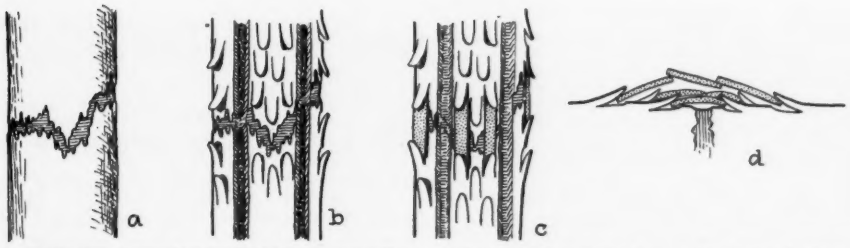


Fig. 4. a, The line of pseudarthrosis is shown, extending across the fusion plate. The articular facets are not represented in this diagram. b, Narrow troughs have been fashioned across the defect, to be filled later with small free bone transplants. Cortical bone chips with bases undetached have been turned up. c, Free transplants are shown wedged underneath the previously reflected bone above and below the defect. d, Longitudinal section showing how the free transplants may be placed in multiple layers and interlocked.

transplant wedged beneath the edge of the bone previously reflected from the plate. Other free transplants may be superimposed in a similar manner. The fusion mass will usually offer a considerable quantity of transplants or they are easily removed from the ilium. The conclusion of the procedure will show a mass of bone transplants wedged onto cancellous bone above and below the defect and extending across it in the longitudinal axis of the fusion plate (Fig. 4).

The previously stripped periosteum is allowed to fall over the bed of bone transplants, sutured, and the incision closed. Depending on the indications for primary fusion, the patient is immobilized with a spine brace or a plaster jacket incorporating both thighs and is kept at absolute bed rest for 8 to 12 weeks. A careful search is then made for possible failure of repair. If fusion has been obtained the patient is allowed up with brace or with an ambulatory jacket. If there is suggestion of failure, immobilization in bed is continued for another 4 weeks. If failure is definitely present, another attempt at repair is then advised.

END-RESULTS

During the period of 1936 through 1945, 1,250 patients underwent operation for spinal fusion. Careful follow up study for at least 1 year after operation was carried out in 1,096 patients. Of this group, the diagnosis of pseudarthrosis was made in 182 patients. The diagnosis was confirmed by exploration of the fusion area in 152 patients. In the remaining 30 patients the diagnosis was established only by applying the standards listed previously, without exploration. In these patients, exploration was advised, but permission was not granted.

During this same period, 23 patients underwent exploration of the fusion mass for failure of fusion, and solid fusion was found. Thus, of 175 patients subjected to exploration, positive evidence of fusion failure was found at operation in the 152 patients remaining or in 86.8 per cent.

One hundred fifty-two patients underwent operation for repair of pseudarthrosis of the spine. All cases have been followed by clinical and roentgenographic examination for at least 1 year. The method of repair which is here described, with minor variations, has been used in the treatment of all patients. Repair was successful primarily in 119 cases, or 78.3 per cent (Table I).

TABLE I.—REPAIR OF PSEUDARTHROSIS

Diagnosis at original fusion	No. patients undergoing repair of pseudarthrosis	No. patients with successful primary repair	Per cent
Scoliosis	51	42	82.3
Lumbosacral instability	51	42	82.3
Lumbosacral instability; internal fixation used at primary fusion	23	17	73.9
Tuberculosis	18	11	66.1
Spondylolisthesis	9	7	77.7
Total	152	119	78.3

Of the 33 cases in which repair was not successful, 16 patients underwent a second attempt at repair and this was successful in 13 cases.

SUMMARY

1. The following findings aid in the diagnosis of pseudarthrosis following the operation for spinal fusion: (a) localized pain and tenderness; (b) progression of deformity or disease; (c) roentgenographic demonstration of fusion failure.

2. In certain cases the diagnosis cannot be established until the fusion plate is explored. We believe that exploration is indicated in every case in which operation did not accomplish the result anticipated.

3. By the technique described, repair of pseudarthrosis is successful primarily in 78.3 per cent of cases.

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AUREOMYCIN TREATMENT OF URINARY TRACT INFECTIONS

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MUCH progress has been made in recent years in the management and cure of many serious conditions along the urinary tract by minimizing or eliminating the factor of infection. The use of acid forming drugs and, more recently, the widespread use of antibacterial agents, particularly the sulfonamides, penicillin, and streptomycin, all of which are excreted into the urine in high concentration and in an active form, have made it possible to limit or eradicate infection in the genitourinary tract without resort to local instillations. It has thus become possible to minimize the need for many of the manipulations and instrumentations which cause additional trauma and may result in the introduction or the further spread of infections.

Failures of chemotherapy and antibiotics are still the rule, however, in severe and long standing infections, especially when there is interference with the free flow of urine or when there are anatomic defects or localized foci of infection within the urinary tract which constantly predispose to reinfection. In addition, the use of streptomycin in such cases, even when care is taken to maintain an alkaline urine, is all too frequently associated with the appearance and persistence of resistant strains which then render that antibiotic entirely useless.

The introduction of a new antibiotic, particularly one which is effective against most of the types of bacteria found in urinary tract infections, is excreted in the urine in effective concentrations, is relatively nontoxic and can be given by mouth, warrants a careful study of its possible usefulness in this field.

Aureomycin is such an agent and this paper presents a clinical and bacteriologic study of its effectiveness in the types of infections which are generally refractory to treatment with other agents or which consistently recur after temporary improvement following the use of the antibacterial agents now available.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

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Choice of patients. The patients selected for treatment with aureomycin were all adults and almost all of them had severe and long standing infections which had failed to respond to treatment. Only 1 patient with a previously untreated acute pyelonephritis complicating pregnancy is included. The others all had various underlying defects along the urinary tract and had been subjected to numerous instrumentations and to various operative procedures either for diagnosis, for relief of symptoms or in an attempt to produce a radical cure. Most of the patients were in the older age groups. Only 4 of the patients, however, were hospitalized during the aureomycin therapy; the others were considered to be especially suitable for ambulatory therapy because they were highly intelligent, completely co-operative, and anxious to be relieved of the infection. Most of the ambulatory patients were referred by Dr. Herbert H. Howard, formerly chief of the Urological Service, who kept these patients under close observation both before and after the aureomycin therapy.

Laboratory studies. Urinalyses were done frequently before, during, and after the aureomycin therapy and included examination of the unstained and stained sediment for cellular elements and for bacteria. These urine specimens, collected by catheterization in females or after careful local preparation in males, were also cultured on various media and the various types of organisms that grew out were isolated in pure culture and tested for sensitivity to the antibiotic. The concentrations of aureomycin in the urines were determined at irregular intervals either in single voided specimens or, in some instances, in

TABLE I.—SUMMARY OF RELEVANT CLINICAL AND LABORATORY FINDINGS

Patient Sex Age	Known duration of urinary infection	Complications, operations, etc.	Organisms previously cultured	Previous chemotherapy	Symptoms before aureomycin therapy	Aureomycin therapy		
						Gm.*	Days	Toxic effects
J.W.C. M 62	3 months	Frequent bleeding; bladder cauterizations; prostatectomy		Sulfadiazine mandelamine	Bleeding, burning, poor control, dysuria	4.5	4½	None
M.C. M 67	5 months	Retention, 2 years; prostatectomy; non-functioning kidney, right; hydronephrosis and hydro-ureter, left.		Sulfadiazine	Nocturia, cloudy urine, back pain	7.0	7	Loose bowels, 3 days
						2 week interval		
						14.0	7	Copious stools 3–7 days
J.A. M 52	12 years	Urethral strictures; dilatations; prostatectomy; acute cystitis; mild diabetes	K. pneumoniae Str. faecalis Esch. coli communis	Sulfadiazine	Dribbling, nocturia, cloudy urine	4.0	4	Frequent large stools
						12 day interval		
						13.0	6½	Same+ urgency
J.C. M 60	2 years	Prostatectomy; incontinence; Cunningham clamp	A. aerogenes Esch. coli P. vulgaris Str. faecalis Staphylococcus Ps. aeruginosa	Sulfadiazine, penicillin, mandelamine streptomycin	Incontinence, burning and dysuria	4.0	4	None
E.F. M 76	>5months; ? many yrs.	Prostatectomy; frequent instrumentation; residual		"Irrigations"	Nocturia, burning	3.0	3	None
K.H. M 56	1 year	Nephrolithiasis, 17 yrs.; urethrotomy; monthly dilatations; bladder residual	Str. faecalis	Sulfonamides, penicillin	Cloudy urine; frequency; burning	8	8	Loose bowels, 3rd day
						16 day interval		
						11.	5½	Nausea, ? dysuria
T.J.M. M 70	>1 year	Numerous instrumentations; prostatectomy; bladder residual	Ps. aeruginosa Esch. coli	Mandelamine, streptomycin	Frequency, dribbling, nocturia	4	4	None
M.N. M 72	15 years	Urolithiasis; nephrectomy 1935; prostatectomy 1944; cystitis; pyelonephritis; residual		Sulfadiazine	Recurrent fever and colic; dribbling; cloudy urine	7	7	None
						12 day interval		
						13.	6½	Nausea
P.D. M 60	3 years	Resection of tumor of left kidney; bladder polyps cauterized	Esch. coli	Sulfadiazine, mandelamine, penicillin, streptomycin	Frequency; burning; nocturia (worse after sulfonamides); poor control	15.5	9	Large frequent stools
W.F. M 32	Since birth	Spina bifida; incontinence; penile clamp; many operations	P. vulgaris, Str. faecalis, Staphylococcus Str. mitior	Sulfadiazine, mandelamine, streptomycin	Incontinence; burning; thick, cloudy urine	9.5	10	Loose bowels, 7 days
						15 day interval		
						7.	3½	Nausea, abdominal discomfort
A.M. M 47	28 years	Nephrolithiasis 28 yrs.; nephrectomy; nephrostomy	A. aerogenes Esch. coli K. pneumoniae	Sulfadiazine, mandelic acid, penicillin	Acute pyelonephritis subsided, pyuria and bacilluria persisted	8.	8	None
R.M. F 24	>1 month	Chronic glomerulonephritis; pyuria after catheterizations			Afebrile and symptomless	6.	6	None
H.M. F 52	2 years	Uterine suspension; wound infection; retention	A. aerogenes Ps. aeruginosa P. vulgaris	Penicillin, sulfadiazine	Frequency, dribbling, dysuria, fever, nocturia, C.V.A. pain	19.	9	None

IN SEVERE URINARY TRACT INFECTIONS TREATED WITH AUREOMYCIN

Bacteriology of urine†					Clinical effects of therapy			Evaluation of effects from aureomycin
Organism	M.I.C.	Relation to therapy			Pyuria		Symptoms and urinary findings	
		Before	During	After	Before	After		
Str. mitior, P. vulgaris	6.3 125.	+ 0	0 0	0 +,3&14	++++	+	Bleeding stopped; less dysuria; cloudy urine 2 weeks later	Slight, temporary
A. aerogenes, Ps. aeruginosa	12.5 200.	+ 0	0 0	0 +,7	++++	+	Less nocturia; partial rapid clearing of urine, recurred 7 days later. Retreated after 2 weeks; again symptomless during and for 1 week after treatment	Moderate, temporary (both times)
Ps. aeruginosa	200.	+	+,3;0,7	+,7	++++	±		
A. aerogenes, P. vulgaris	6.3 250.	+ 0	+,2;0,4 0	0 +,5	++++	±	Felt generally better; less nocturia; cloudy urine and symptoms returned after 7 days; felt better during second course	Slight, temporary
P. vulgaris	250.	+	+,3&7	+	++++	+++		None
P. vulgaris	125.	+	+,1; 0,2&4	0,4; then +	++++	0	Burning stopped; bladder control better; less dribbling	Moderate, temporary
A. aerogenes	6.3	+	0	0,5&12	+++	0	Much improved; no symptoms	Good
Esch. coli, P. vulgaris	12.5 125.	+ 0	+,1;0,3–7 0	0 +,2&6	+++	±	Urine cleared but again got cloudy; some frequency and burning after second course which then cleared (along with proteus) on sulfadiazine.	Slight, temporary (both times)
A. aerogenes, P. vulgaris	25. 125.	+ 0	0 0	0 +,2	++	0		
Esch. coli	12.5	+	0	0	++	0	No nocturia; less dribbling	Good
Esch. coli, A. aerogenes	12.5 100.	+ 0	+,3&5 0	+ +,2	+++	+	Urine cleared for 6 days after treatment, then got cloudy again; improved after second course	Slight, temporary; more from second course
Esch. coli, A. aerogenes	25. 50.	+ 0	0 0	0 +,2	+++	±		
Esch. coli, Ps. aeruginosa, A. aerogenes	12.5 200. 12.5	+ 0 0	+,3; then 0 0 0	0 +,1 +,14	+++	+	Less nocturia and frequency; burning almost gone; better control	Slight, temporary
P. vulgaris	200.	+	+	+	+++	+	Improved, less burning and urine clear after first course; relapsed and again improved after second course	Slight, temporary (both times)
P. vulgaris Esch. coli	250. 25.	+ +	+ 0	+ 0	++	+		
A. aerogenes	25.	+	+,4;then 0	0	++	0	Pyuria cleared rapidly	Good
Esch. coli	100.	+	0	0	++	0	Pyuria cleared	Good
Esch. coli, Ps. aeruginosa, P. vulgaris	6.3 >200. 250.	+ + 0	+,2 +,5 +,5		+++	+	Almost complete symptomatic relief; bladder emptied well; no follow-up	Moderate, incomplete

TABLE I.—SUMMARY OF RELEVANT CLINICAL AND LABORATORY FINDINGS IN

Patient Sex Age	Known duration of urinary infection	Complications, operations, etc.	Organisms previously cultured	Previous chemotherapy	Symptoms before aureomycin therapy	Aureomycin therapy		
						Gm.*	Days	Toxic effects
S.F. F 22	6 days	Pregnancy; acute pyelonephritis			Frequency, burning, flank pain	6.	4	None
R.M. M 28	3 years	Bilateral ureterolithotomy; nephrectomy, right; nephrostomy, left; appendicitis with perforation and peritonitis. Readmissions for abdominal abscess; indwelling catheter after operation	A. aerogenes, Esch. coli Ps. aeruginosa	Sulfadiazine, penicillin, streptomycin	C.V.A. pain; cloudy urine; malaise	7.	7	Loose stools; nausea once
						11 week interval		
					Cloudy urine	23.	17	Nausea, vomiting; stopped when dose reduced
D.C. F 27	2 months	Diabetes; cesarean section; intractable cystitis	Esch. coli	Sulfadiazine, mandelamine, penicillin, streptomycin	Back pain, frequency, cloudy urine, chills, fever, malaise	4.	4	Loose stools, nausea
						25 day interval		
						28.	28	None

*Total amount listed; mostly given in 0.5 gm. doses morning and night or before each meal and at bedtime.
†M.I.C.—inhibiting concentration (complete) of aureomycin in μg./ml.; +=positive, o=negative for organism indicated. All strains of the same begun and after treatment ended in columns "during" and "after," respectively.

urine collected over periods of several hours. The methods are described elsewhere (1, 3).

Aureomycin treatment. The antibiotic was provided as a powder in capsules, each containing 50 milligrams, and was given by mouth. Most of the patients received 10 capsules (0.5 gm.) morning and night for about a week, but 0.5 gram 4 times a day (before each meal and at bed time) was given for varying periods in some of the patients and in almost all of those who were given a second course.

RESULTS

The relevant clinical and laboratory findings, the therapy used, and an evaluation of its effect in each of 16 patients is shown in Table I. In 7 of these patients a second course of aureomycin was given, usually after an interval of 2 weeks, either because the infection was not completely eliminated or because it recurred.

All but 1 of these patients had a chronic and recurrent infection of the urinary tract which, in most instances, was of several years' duration. Almost all of them had a long history of severe complicating factors, such as urinary retention, frequent instrumentations, prostatectomy, urolithiasis, and chronic and recurrent acute cystitis and pyelonephritis. In almost all instances, one or more chemotherapeutic or antibiotic agents had been used previously without producing prolonged remissions. Thus, the least favorable types of cases were chosen for evaluation of the effects of aureomycin.

The predominant clinical symptoms prior to the aureomycin therapy were dysuria, poor sphincter control, frequency, nocturia, and cloudy urine. Some had had recurrent attacks of severe costovertebral angle pain and tenderness. The urine was loaded with pus cells in every case.

In general, the pyuria diminished markedly during therapy and disappeared entirely in about half of the patients while treatment was still being given. Symptomatic relief occurred at the same time in most instances, the burning on urination, frequency, and nocturia all diminished or subsided.

The urine became highly acid and remained so throughout the treatment. Cultures obtained immediately before treatment usually revealed only a single strain of organism but in those who received a second course of aureomycin, organisms other than those initially present had appeared during or after the first course. The cultures usually became sterile during the aureomycin treatment. In some of

SEVERE URINARY TRACT INFECTIONS TREATED WITH AUREOMYCIN—Continued

Bacteriology of urine					Clinical effects of therapy			Evaluation of effects from aureomycin
Organism	M.I.C.	Relation to therapy			Pyuria		Symptoms and urinary findings	
		Before	During	After	Before	After		
Esch. coli, A. aerogenes	25. 12.5	+ +	o +,1; then o	o o	+++	o	Fever subsided and urine cleared promptly; afebrile in 2 days	Good
A. aerogenes K. pneumoniae P. vulgaris	25. 50. 125.	+ + o	+,3; then o +,1; then o +,5–7	o o +,12; then o	++++	o	Improved and remained well with clear urine until readmission for abdominal abscess; urine cleared rapidly	Good, first course; moderate second course
Ps. aeruginosa, P. vulgaris	250. 125.	+ o	+ +,10	+ o	++++	±		
Esch. coli	6.3	+	+	+	++	o	Asymptomatic until 10 days after first course when all symptoms returned; again symptomfree after retreatment until 10 days after second course	Moderate and temporary (both times)
Esch. coli	6.3	+	+,8; then o	+,14	++	±		

organism isolated in the same patient had the same sensitivity to aureomycin. The numbers after "+" and "o" indicate the day after treatment

the patients, however, Proteus vulgaris or Pseudomonas aeruginosa and in 2 instances Escherichia coli either first appeared or persisted during aureomycin treatment. Infection recurred within a few days in most instances, with either the same or with different organisms. The proteus organisms were the most persistent but pseudomonas also could not be eradicated.

Good results of a permanent nature were, therefore, infrequent in these cases of chronic urinary tract infections. Temporary relief, either slight or moderate, resulted in about two-thirds of the patients. The patient with the acute pyelonephritis complicating pregnancy responded promptly with both symptomatic relief and a bacteriologic cure.

Sensitivity of organisms. As seen in Tables I and II, most of the organisms were quite sensitive to aureomycin. Most of them were completely inhibited by concentrations ranging from 6.3 to 50 micrograms per milliliter, but the strains of proteus and pseudomonas required 125 to 250 micrograms per milliliter for complete inhibition. Partial inhibition usually occurred in one-half or one-fourth of the concentrations which were needed for complete inhibition. It is seen from Table II that the more resistant organisms are the ones which persisted or appeared in the cultures during and after the aureomycin treatment. All of the strains of the same organism that were isolated from the same patient, however, were equally sensitive to aureomycin. There was no evidence of any tendency for resistant variants to develop during therapy.

Aureomycin levels. The methods available were rather crude (1, 3). The aureomycin activity in the urine that was demonstrated by these methods was equivalent to concentrations of 32 to 256 micrograms per milliliter in specimens of urine obtained during treatment and between 2 and 12 hours after a dose of 0.5 gram. Of interest is the fact that concentrations of 16 micrograms per milliliter, and sometimes more were obtained as long as 48 hours after the last dose and smaller concentrations were demonstrable for more than 72 hours. The errors involved in the methods were such as to suggest that the actual concentrations were considerably higher, since the antibiotic tends to deteriorate rapidly on standing and even during the course of the tests. Blood levels were usually 2 micrograms per milliliter or less but concentrations of 8 micrograms per milliliter were obtained in 1 patient while he was receiving 1 gram every 12 hours.

TABLE II.—SUMMARY OF BACTERIOLOGIC FINDINGS IN THE URINE IN RELATION TO AUREOMYCIN THERAPY

Organism	Sensitivity μg.-ml.	No. of patients*	Relation to aureomycin therapy†		
			Before	During	After
Streptococcus mitior	6.3	1	1	0	0
Klebsiella pneumoniae	5	1	1	1	—
Aerobacter aerogenes	6.3–100	9^1	7	4	3‡
Escherichia coli	6.3–100	9^2	11	6	3
Pseudomonas aeruginosa	200–250	4^1	3	3	4
Proteus vulgaris	125–250	7^4	4	8	9

*Superscripts indicate the number of patients included from whom the same organism was isolated in relation to 2 separate courses of aureomycin.
†The figures denote numbers of patients; those receiving 2 courses are listed separately in relation to each course.
‡Two of these yielded the only strains that required 50 or 100 μg. per ml. to inhibit.

Toxic effects. These were minimal. The most common complaint was looseness of the bowels with frequent (2 to 4 daily), bulky, and soft stools but not true diarrhea. This was more frequent and was accompanied by some nausea and occasional vomiting when doses of 2 grams a day were given. In some of the patients with cystitis, a disagreeable sensation as of something "drawing" or "squirming" in the pelvis was sometimes noted. This may have been related to the high acidity of the urine during ingestion of large doses of aureomycin. There were no other symptoms in these or in other patients, nor was there any laboratory evidence of renal or liver damage or of any toxic effects on the blood. There were no fevers or rashes attributable to the antibiotic.

COMMENT

These cases were chosen deliberately because, with the exception of the patient with acute pyelonephritis, they represent the types of urinary tract infection which are usually refractory to the chemotherapeutic and antibiotic agents that are now available. When all of the clinical and bacteriologic findings are taken into account, the results in these cases may be considered to be quite satisfactory, although they still leave much to be desired. The results are probably as good as, if not better than, those usually obtained in similar cases with sulfonamides or with streptomycin. Since most of these patients had previously proved refractory to these agents and some were relieved of symptoms and pyuria for the first time in many months while they were taking aureomycin, this agent may prove to be a useful addition to the therapy of urinary tract infections. Aureomycin has several advantages over other agents used in this field in that it can be given by mouth, it is effective against infections with both gram-positive and gram-negative organisms (2) and from present indications it can be given for long periods without significant toxic effects and without giving rise to resistant variants (2, 3). It is relatively ineffective, however, against infections with Proteus vulgaris and with pyocyaneus.

CONCLUSIONS

Aureomycin may prove to be a useful addition to the list of agents that are effective in the treatment of urinary tract infections and should have further clinical trials in such infections.

ADDENDUM.—Since this paper was submitted for publication, more than 50 additional patients with urinary tract infections have been treated with oral aureomycin. One-third of these patients had acute pyelonephritis, cystitis, or both, and all but 1 of these patients were completely cleared of bacteriuria and pyuria. The results in the chronic cases were similar to those noted in the cases presented here.

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STUDY ON THE RELIEF OF OBSTRUCTION IN THE COMMON BILE DUCT AND IN THE PAPILLA OF VATER

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THE problem of obstruction at the terminal end of the common bile duct has been prominent for many years. The surgeon meets this condition all too frequently, and on occasion he is hard put as to know what to do. Those patients who have had cholecystectomy, with or without choledochotomy, and who subsequently develop evidence of obstruction to the flow of bile from the common bile duct into the duodenum have been responsible for much aggravation for the surgeon. The obstructions to be considered at the present time are those resulting from spasm at the papilla of Vater, and from stones or mucous plugs in the common bile duct.

The presence of a sphincter mechanism at the termination of the common bile duct was noted by Oddi in 1887. Careful anatomical studies by Kirk and by Schwegler and Boyden leave little to be added along this line of investigation. Much has been written regarding the physiology of the sphincter of Oddi, reporting the effect of certain drugs upon the state of the sphincter and the duodenum, but with varying and at times controversial results (1, 2, 4, 6, 7, 8, 10-12, 14, 15, 20-22, 25, 26, 32). Various methods have been described and advocated, in an effort to dislodge or dissolve the obstructing factor, be it stone or mucous plug (3, 5, 13, 17, 18, 23, 24, 29, 30). Such obstructions at the terminal end of the common bile duct may be relieved by either surgical or nonsurgical methods. The surgical approach to the problem is obvious, but in many instances reoperation may not be advisable. One may consider several different approaches, namely, an attempt to enlarge the tube through which the obstructing agent must pass, an attempt to increase the hydrostatic pressure within the common bile duct proximal to the obstructing agent, thereby forcing it into the duodenum, or a combination of the two. The hydrostatic pressure in the common bile duct may be increased by perfusing solutions through a drainage tube or by the administration of hydrocholeretics which usually result in the outpouring by the liver of a large amount of thin watery bile. The terminal end of the common bile duct may be enlarged by the use of certain drugs, in an effort to produce relaxation of the sphincter of Oddi and duodenum, or possibly an actual paralysis of the sphincter and duodenum as will be seen later. Our problem was, therefore, divided into several parts: (a) a study of the effect of certain drugs upon the state of the sphincter of Oddi and duodenum, (b) a study of the site of action of these drugs and, (c) an attempt to duplicate the problem in the laboratory animal as it appears in the human.

Our preparation was similar to that of Kozoll and Necheles (17), Necheles (25) and Crohn and associates (9). Figure 1 illustrates diagrammatically the animal preparation. Dogs with an average weight of 10 kilograms were anesthetized with sodium pentobarbital. Carotid blood pressure was recorded. The pylorus was ligated and gastric secretion was evacuated through a drain. The common bile duct was cannulated *in situ*. One cannula in its proximal end served to evacuate bile. A second cannula, inserted approximately 2 centimeters from the papilla of Vater and pointing toward the duodenum, was connected by a T tube to a constant infusion pump (27) and to a recording mercury manometer. The solutions which were perfused through the common bile duct at a rate of 2 cubic centimeters per minute were evacuated through a tube in the duodenum, 2 to 3 centimeters distal to the papilla of Vater. Following a control

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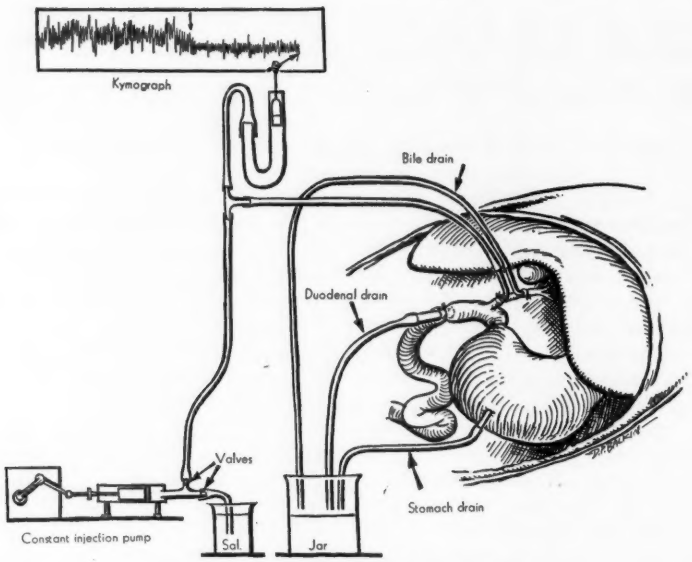

Fig. 1. Experimental preparation. See text.

period, the saline perfusate through the distal common bile duct was replaced by the test drug dissolved in 100 cubic centimeters of saline. The time of perfusion with each drug was approximately 10 minutes, after which time saline perfusion was resumed. In an effort to duplicate what may often occur in the human with biliary tract disease, it was decided to maintain the sphincter of Oddi in a state of spasm. This was accomplished by constant slow intravenous injection of a saline solution of prostigmine, at the rate of 0.1 milligram of the drug per hour.

Changes in rhythmic motility and tone of the sphincter of Oddi are graded as + to ++++. + Denotes a diminution of rate of rhythmic contractions but not of their height. ++ Denotes diminution of rate and slight diminution of height of the contractions. +++ Denotes distinct diminution of both and drop of tone. ++++ Denotes drop of tone and abolition of motility, i.e., complete patency of the sphincter. Nontoxic doses of all drugs were employed. The percentage of effectiveness denotes the per cent incidence of relaxation of the sphincter in all experiments with a given drug.

The drugs which may have an effect on the sphincter of Oddi can be grouped into two categories. The group of topic or local anesthetic drugs were considered as being of possible benefit because of their interference with sensory receptors and afferent branches of reflex arcs, with subsequent release of spasm and subsidence of edema (LeRiche and Crohn and associates). The second large group of drugs includes those responsible for smooth muscle relaxation, either by direct effect on the smooth muscle or by abolishing cholinergic nerve action. Many drugs were tested in an effort to find the one which afforded consistently good results. The drugs were administered intraductally in saline solution or they were given intravenously. The following local or topic anesthetic drugs were tested: procaine, nupercaine, butyn, cocaine, metycaine. The following antispasmodic or spasmolytic drugs were tested: papaverine, trasentin, atropine, homatropine methyl bromide, dibutolene, amyl nitrite, aminophylline; some spasmolytic drugs have also local anesthetic effects, e.g. trasentin.

In the first group of experiments, drugs were tested by means of perfusion through the

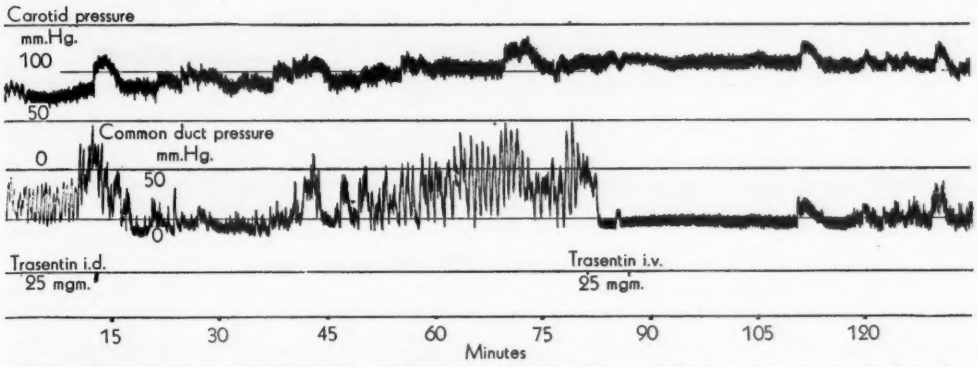

Fig. 2. Experiment 10, male dog weighing 12 kilograms. Effect of trasentin. ++ Response after perfusing 25 milligrams of trasentin through the common bile duct. +++ Response following intravenous injection of 25 milligrams of trasentin.

common bile duct and part of the duodenum. The results were graded as described before. There was a latent period following perfusion of the drugs which varied from a few seconds to 11 minutes from the time of completion of the perfusion. The latent periods, for the same dose of the same drug, varied in the same animal in a number of experiments. However, in most tests the latent periods were rather short. The duration of drug effect also varied in the same animal with the same dose of the same drug. A ++++ response may persist for 25 minutes on one occasion whereas another ++++ response may persist for 74 minutes. It was also noted that at times a ++ response would last longer than a ++++ response, again using the same dose of the same drug in the same animal. Because of the constancy of the dosage and infusion, it must be assumed that these are variations peculiar to the animal being used at the time. The blood pressures, as recorded, did not vary as a result of perfusion of the test solution through the duct. Of all the drugs used intraductally, the only one which gave results consistently was papaverine, which was graded 100 per cent. Atropine and homatropine methyl bromide were graded 50 per cent, procaine 47 per cent, trasentin 44 per cent, and aminophylline 33 per cent, effective. The other drugs tested, nupercaine, metycaine, butyn, dibutolene, sodium nitrite, and cocaine, were found ineffective. The effect of amyl nitrite was rather interesting in that a ++ response was obtained by the perfusion of a saline solution of the drug; the perle having been crushed under saline. However, the result could not be duplicated, even when a crushed perle was held to the animal's nose or tracheal cannula.

In the second group of experiments, drugs were used intravenously. The dog preparation was the same as used before. The drug was injected over a period of 10 minutes and its effect, when present, was seen as soon as the injection was completed and frequently even before completion. The latent periods were shorter with intravenous administration. The length of effect varied in this series as it did when the drugs were perfused through the common bile duct. Also, identical doses of the same drug produced effective changes in the intraductal pressure which were either longer or shorter than the changes produced when the same drug was given intraductally. The duration of effect, using the same dose of the same drug in the same animal, varied; for instance, a +++ response persisted for 62 minutes whereas a ++++ response persisted for 38 minutes. However, there seemed to be a more constant relation in this series of tests between the degree and the duration of effective response, i.e., the greater the degree of response, the longer the effect. It was also noted that there was a tendency for the blood pressure to drop during the injection of the

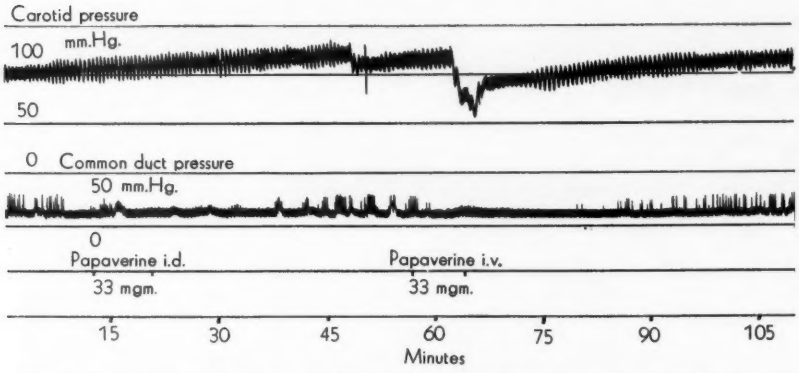

Fig. 3. Experiment 11, male dog weighing 12.2 kilograms. Effect of papaverine. +++ Response after perfusing 33 milligrams of papaverine through the common bile duct. ++++ Response following intravenous injection of 33 milligrams of papaverine.

test drug or during its period of effectiveness. This could be kept at a minimum by administering the drug slowly and in a dilute solution. In this series papaverine was again rated as being 100 per cent effective. Atropine, homatropine methyl bromide and dibutolene were also rated as 100 per cent, the latter having been used only once. Aminophylline was graded 75 per cent, trasentin 66 per cent, and procaine 41 per cent. The remainder of the drugs tested intravenously, nupercaine, metycaine, butyn, and cocaine, were graded 0 per cent.

Several drugs were tested which have been known to increase intraductal pressure and several others whose specific effect had not yet been determined. These drugs also tested the responsiveness of the sphincter of Oddi and duodenum in a number of experiments. Codeine phosphate, given subcutaneously or intravenously, produced an elevation of intraductal pressure, probably as a result of contracting the sphincter of Oddi and duodenum. Demerol was also tested and found to react in a similar manner, although the effect was not as marked. Adanon, which is said to have a morphine like action, produced an increase in the intraductal pressure.

Figure 2 illustrates the effect obtained after the administration of trasentin intraductally and intravenously. Twenty-five milligrams of the drug were perfused through the common bile duct and a ++ response was obtained which persisted for about 30 minutes. A +++ response was obtained after the intravenous administration of the same dose of drug, persisting for about 25 minutes. It will be noted that there was no lowering of the blood pressure after either test.

Figure 3 illustrates the effect obtained after the administration of papaverine intraductally and intravenously. Thirty-three milligrams of the drug were perfused through the common bile duct and a +++ response was obtained which persisted for about 30 minutes. A similar dose administered intravenously resulted in a ++++ response persisting for 30 minutes. It will be noted here that the blood pressure was not lowered during the intraductal administration of the drug, but that a temporary lowering did occur following the intravenous injection.

Figure 4, in a similar experiment, demonstrates the effect of 1 milligram of homatropine methyl bromide (Maltbie) when perfused through the common duct, and a much more profound and long lasting effect of half of the dose of the drug given intravenously; there was hardly an effect on the blood pressure.

The question of site of action of these drugs soon arose. Because of the fact that the latent periods proved to be shorter following the intravenous injection than following intraductal perfusion of the drug, it was surmised that perhaps the drugs when perfused through the common bile duct, produced their effects after

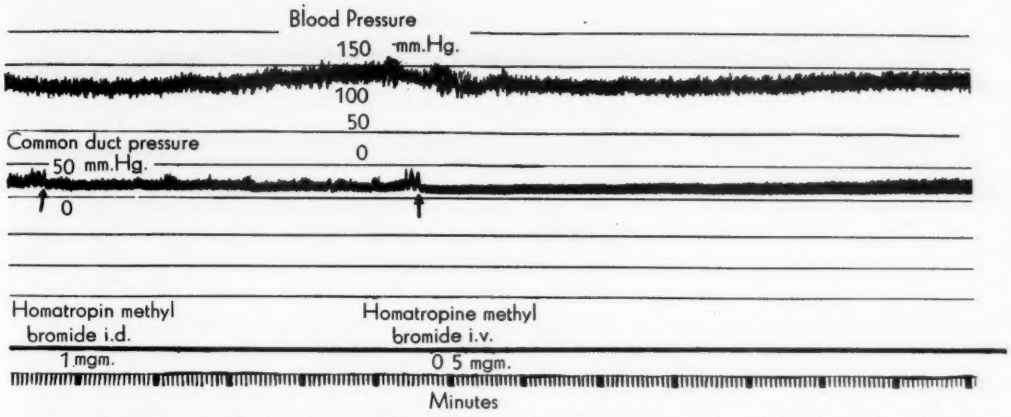

Fig. 4. Dog M, weighing 14 kilograms. July 26, 1947. Nembutal anesthesia. Effect of homatropine methyl bromide. Positive effect following perfusion of 1 milligram of homatropine methyl bromide (Maltbie) through common duct. Very prolonged ++++ effect following intravenous injection of ½ milligram of same drug. Homatropine methyl bromide was a very effective intravenous drug for relaxation of sphincter of Oddi and duodenum.

absorption from the duodenum. A modification of the dog preparation was instituted. In addition to the preparation described, the duodenum was incised on its antimesenteric border, in the region of the papilla of Vater. The papilla was visualized and covered with one end of a soft rubber tube with a lumen of 0.5 centimeter. An inverted U stitch was placed in the rubber tube, brought out through the duodenal wall away from the papilla, and tied gently over a button, thereby anchoring the tube over the papilla. The other end of the rubber tube came out through the incision in the duodenum and drained into a glass jar. Tests with dyes showed that the duodenum had been excluded from the flow of the perfusion fluid and absorption by the duodenal mucosa of solutions perfused through the common bile duct was therefore minimal. Solutions of papaverine, butyn, procaine, trasentin, aminophylline, atropine, and ether, were perfused through the common bile duct and their effects on intraductal pressure recorded. All drugs were ineffective. At the end of each experiment in this series a drug which was known to decrease intraductal pressure was given intravenously as control. It was reasoned that, if several drugs known to be effective when given intravenously had been perfused through the common bile duct and found to be ineffective, and if an effective result was obtained by a known effective drug given intravenously, we had proved the site of action of these drugs. Figure 5 illustrates an experiment in this series. Solutions of aminophylline, papaverine, procaine and trasentin were perfused through the common bile duct and produced no effective response, whereas the intravenous injection of 50 milligrams papaverine produced a ++++ response. Papaverine, because of its 100 per cent effectiveness was used at the end of three experiments; aminophylline was used once. Both drugs, when given intravenously, proved to be very effective, after no results had been obtained when the drugs were perfused through the common bile duct. This group of experiments led us to believe that whatever good results we had previously obtained by means of perfusion of drugs through the common bile duct occurred as a result of absorption via the duodenal mucosa, rather than by direct action upon the papilla of Vater. These findings corroborated the fact that the duodenum has great absorptive power in spite of the fact that the perfused solutions spent so little time in that organ.

The next phase of our problem was an attempt to duplicate human pathology in the laboratory animal, the production of an obstruction of the common bile duct. The dog preparation was essentially the same as used

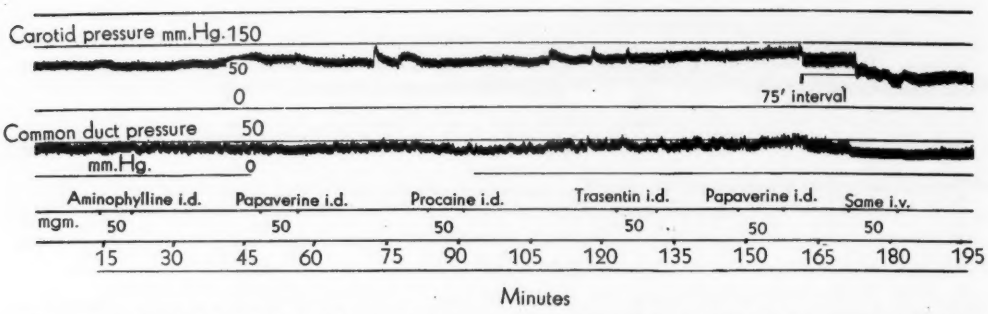

Fig. 5. Experiment 26, female dog weighing 13 kilograms. Papilla of Vater covered and duodenum excluded. No effective response of intraductal pressure following perfusion of drug solutions through the common bile duct. ++++ Response following intravenous administration of papaverine.

in the first series of experiments except for the fact that small gall stones or small pieces of gravel were placed into the distal segment of the common bile duct before the cannula was inserted. Gravel was used in the smaller common ducts whereas gall stones were used in the larger ones. The dog preparation allowed us to use one or both of the methods mentioned earlier in an effort to produce passage of the obstructing agent into the duodenum. We were able to increase the hydrostatic pressure within the common bile duct proximal to the obstructing agent by means of perfusion pressure or by the intravenous administration of decholin, and we were able to produce relaxation of the sphincter by the intravenous administration of the most effective drug tested earlier. Seven dogs were used for this group of experiments. In dog 27, whose kymograph tracing is presented in Figure 6, two gall stones were inserted into the common bile duct and passed rather quickly into the duodenum under influence of the perfusion pressure. The same occurred after another stone had been inserted. However, a third and larger pair was inserted and passage of these did not occur until we had increased the perfusion pressure and had administered 50 milligrams of papaverine intravenously. In dog 4 a stone was placed into the common bile duct, but the hydrostatic pressure was increased by the intravenous administration of decholin. Decholin was given at intervals of 15 minutes and papaverine was given every 30 minutes. The duodenum was opened at the end of about 2½ hours. Examination revealed the stone to be nearly through the papilla of Vater, with about 75 per cent of its mass protruding into the duodenum. If we had waited a bit longer there was every reason to have expected to find the stone entirely within the duodenum. A rather large piece of gravel was placed into the common bile duct of dog 6 and it did not move in spite of decholin and papaverine intravenously and procaine perfused through the common bile duct and the duodenum. Obviously the foreign body was too large for this common bile duct to pass. Several insertions of stones were performed in dog 33. These stones passed into the duodenum under influences of the perfusion pressure. A fifth stone did not pass with perfusion pressure alone. Following the use of papaverine, the intraductal pressure suddenly rose and soon dropped, followed by passage of the stone into the duodenum. This phenomenon may be explained by the stone passing along the common bile duct, meeting the sphincter and causing a rise in the intraductal pressure. The pressure dropped and the stone was passed into the duodenum.

DISCUSSION AND CONCLUSIONS

The problem of obstruction at the terminal end of the common bile duct is interesting, but often is difficult to manage. Our efforts have been directed toward the search for a safe, comparatively easy method for removal of these obstructions, and one which will afford a good chance of success. The investigation

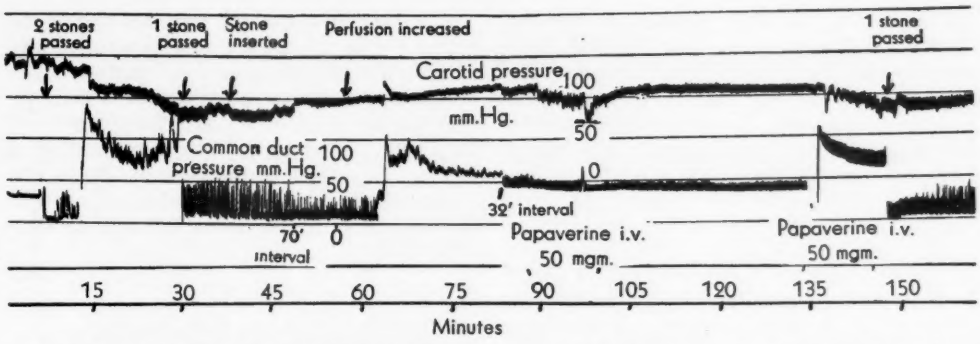

Fig. 6. Experiment 27, male dog weighing 14 kilograms. Stone experiment. Stones passed into the duodenum twice under influence of the infusion pump. Third stone did not pass into the duodenum after increasing the perfusion pressure, but did pass into the duodenum after second administration of papaverine.

divided itself into three parts, namely: (a) a study of the effects of certain drugs on the terminal end of the common bile duct, (b) a study of the site of action of these drugs, and (c) an effort to duplicate in the laboratory animal what may appear in the case of stones in the common bile duct of the human. We searched for the drug which, when given into the common bile duct or when injected intravenously, would have a relaxing effect upon the sphincter of Oddi. Two large groups of drugs presented themselves for consideration, the local or topic anesthetic group and the antispasmodic or spasmolytic group. Many members of each group were tested and we found that papaverine gave us the most constant relaxing effect upon the sphincter of Oddi. Papaverine worked equally as well given intravenously or when perfused through the common bile duct. Papaverine has been previously tested by other authors and found to give inconstant results, but in our hands it seemed to be the most reliable of all drugs used. This discrepancy lies probably in the fact that the dose used had been too small. Recent laboratory and clinical studies have emphasized the fact that papaverine must be given in sufficiently large doses to produce the desired effect. The local or topic anesthetic group of drugs seemed to be promising early in our study, but as repeated experiments were carried out they seemed to be less reliable than the antispasmodic group. Other drugs gave results similar to those obtained with papaverine, but it seemed to us that papaverine proved to be the drug of choice, because of its reliability in producing a prolonged relaxation of the sphincter of Oddi and duodenum.

The problem of the site of action of the drugs used was then investigated. We set out to prove whether a drug acted upon the sphincter of Oddi after absorption through the duodenal mucosa, when it was perfused through the common bile duct, or whether it had a direct action upon the terminal end of the common bile duct. By a method of completely covering the papilla and thereby blocking out the duodenum, we were able to answer this question. It was found that drug solutions perfused through the common bile duct and papilla of Vater, the latter having been covered and excluded from the duodenal mucosa, had no effect upon the sphincter of Oddi, whereas the same drug had a good relaxing effect upon the sphincter of Oddi when given intravenously. This series of experiments led us to believe that the effect upon the sphincter of Oddi by the drug solutions perfused through the common bile duct was produced after absorption had taken place from the duodenal mucosa and not because of a direct action of the drug upon the terminal end of the common bile duct. We were also impressed by the marked absorptive power by the duodenal mucosa of a drug solution which spent so little time in a small section of that organ.

The final part of our problem resolved itself in an effort to duplicate human pathology in

the laboratory animal. Stones of varying sizes and shapes were inserted into the distal common bile duct and various methods were studied by which they could be made to pass into the duodenum. It seemed reasonable to assume that stones would pass if one of three methods were utilized; building up the hydrostatic pressure within the common bile duct. relaxing the terminal end of the common bile duct, and a combination of the two. The hydrostatic pressure was increased by either perfusing solutions through the common bile duct or by the administration of decholin, which resulted in an increased flow of thin watery bile. The terminal end of the common bile duct was relaxed by the intravenous administration of adequate doses of papaverine. We found the common bile duct to vary considerably with individual animals and on several occasions many insertions of increasingly larger sized stones were necessary in order to test our methods. Some of the stones were forced into the duodenum by the infusion pump running at normal speed, whereas other stones did not pass until the perfusion stroke volume had been increased. The experiments wherein the stones did not pass under the effect of the infusion pump but finally passed when papaverine was given, proved quite satisfying to the observer. Careful experiments on patients will have to determine which of the above procedures are applicable to the human and particularly, what perfusion pressure through a drained common duct can be employed.

SUMMARY

1. Certain drugs, when perfused through the common bile duct, can lower the intraductal pressure by their relaxing effects upon the sphincter of Oddi and duodenum.

2. Papaverine seemed to be the drug of choice. It produced the most constant results when given in large enough doses.

3. The drugs used do not act directly upon the terminal end of the common bile duct. When perfused into the common bile duct they exert their effect after absorption through the duodenal mucosa.

4. Obstructions at the terminal end of the common bile duct, produced experimentally by insertion of stones, were relieved by either increasing the hydrostatic pressure within the common bile duct, by relaxing the sphincter of Oddi and duodenum or by a combination of the two. Pressure in the common ducts was increased either by administration of a hydrocholagogue, or by perfusion through the cannulated distal common duct.

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INTRATHORACIC GOITER LOCATED IN THE POSTERIOR MEDIASTINUM

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IN spite of the existence of an extensive literature on the subject of thyroid disease, there remains considerable misunderstanding regarding the development and characteristics of intrathoracic goiter. The terms substernal and intrathoracic goiter are often confused and are sometimes considered to be synonymous. An understanding of the anatomical relations of the several types of intrathoracic goiter is of great importance to the surgeon in the differentiation of these terms.

In the majority of cases when a goiter extends into the thorax, the enlarging gland pushes downward and forward so that its lowermost portion lies ultimately in the superior mediastinum just beneath the sternum. It is rare in such a condition for the tumor to lie almost completely within the chest. There is usually a large component of the gland in the neck as well. The term substernal goiter used to designate such an arrangement is only partially correct and to speak of such goiters as being intrathoracic is somewhat misleading. In true intrathoracic goiter, on the other hand, the largest diameter of the tumor lies in the mediastinum below the thoracic inlet. The majority of these lie anteriorly, but in a few cases the mass descends into the posterior portion of the mediastinum, a situation which has rarely been referred to in the literature. Its importance lies in the fact that such posteriorly placed goiters are often erroneously thought to be primary mediastinal tumors, and in the fact that if they become very large they can be removed only through a thoracotomy incision.

Anatomical considerations. Posteriorly placed intrathoracic goiters always have a pedicle-like connection with the thyroid gland in the neck, but this attachment is frequently small. They lie at the farthest posterior aspect of the mediastinum against the vertebral column. They tend to press the esophagus to the right or left but as a rule they do not disturb the relations of the trachea to as great an extent. A slight forward displacement of the trachea, however, is often observed. As they increase in size they enlarge downward and laterally. When they are very large, they encroach considerably upon the space occupied by the upper lobe of the lung on the side where they happen to lie (Cases 5 and 6).

It has been said that an intrathoracic goiter always retains a position anterior to the recurrent laryngeal nerve and to the inferior thyroid artery. This is correct only in the case of those which descend into the anterior mediastinum and are therefore merely substernal. The goiters which enter the posterior mediastinum lie behind these structures. Furthermore, there is an important difference between the two types of goiter, depending upon their relations to the carotid sheath, the innominate and subclavian arteries, the innominate veins, and, on the right, the superior vena cava. Anteriorly placed substernal goiters always descend in front of these vessels. Posteriorly placed intrathoracic goiters, on the other hand, always descend behind them.

The reason for the differences between the anatomical relations of the two types of intrathoracic goiter is a simple one. Substernal and anteriorly placed intrathoracic goiters arise either from the lower poles of the lateral thyroid lobes or from the isthmus. As they enlarge and extend downward, they push the trachea and esophagus posteriorly and laterally and always lie in front of the recurrent laryngeal nerve, the inferior thyroid artery, the innominate veins, the innominate and subclavian arteries, and to some extent the carotid sheath. The fact that posteriorly placed goiters descend behind these structures is explained by the fact that such goiters arise not from the inferior pole of the lateral lobe of the gland but from its posterior and lateral aspect.

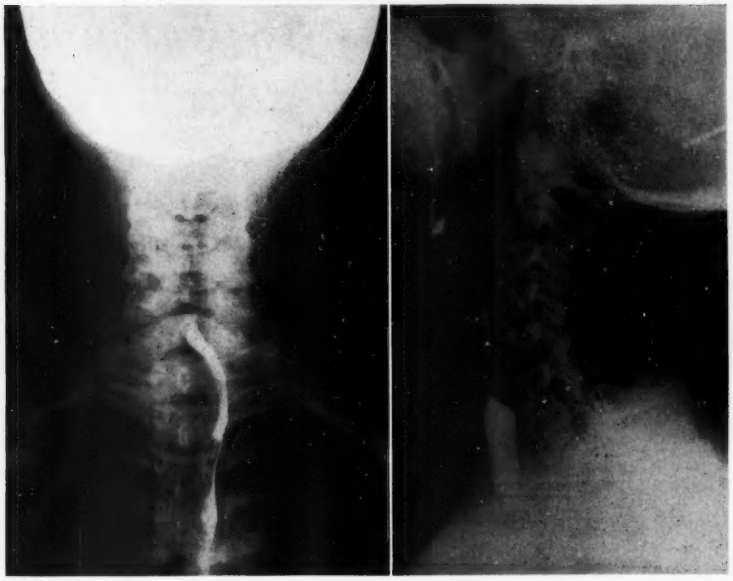

Fig. 1, left. Case 1. Anterior roentgenogram showing marked deviation of the esophagus produced by small intrathoracic goiter with relatively little tracheal displacement.
Fig. 2. Case 1. Lateral roentgenogram showing slight anterior deviation of the trachea at the base of the neck.

The validity of this explanation based upon the site of origin of the goiter in the gland itself is strongly suggested by the findings at operation in 3 of the 6 cases reported. In Case 1 the preoperative roentgenogram showed marked displacement of the esophagus to the left side and only slight displacement of the trachea forward and to the left. At operation, performed through the usual cervical thyroidectomy incision, the lower pole of the right lobe was uninvolved, but the goiter, which was relatively small, had arisen from the posterolateral surface of the lobe and had enlarged downward a short way into the mediastinum but definitely behind the carotid sheath and the recurrent laryngeal nerve and inferior thyroid vessels. The situation in this case represented an early phase in the development of a posterior mediastinal intrathoracic goiter. Removal was accomplished easily through the cervical incision (Figs. 1 and 2).

Case 2 represents a further stage in the process. In this case the goiter arose from the left lateral lobe and descended posteriorly and to the left, pushing the esophagus and trachea to the right. At operation it was demonstrated that the enlargement had arisen from the lateral aspect of the left lobe well above the lower pole. It had descended behind the recurrent laryngeal nerve and inferior thyroid vessels as well as the carotid sheath and left subclavian vessels, lodging finally in the posterior mediastinum against the anterior surfaces of the upper thoracic vertebral bodies. It bulged into the left pleural cavity but was relatively easily removed through the cervical incision. In this case the mass was larger and had extended much further downward and posteriorly than in Case 1 (Figs. 3 and 4).

Case 3 is of particular importance in demonstrating the origin and anatomical relations of a posteriorly descended intrathoracic goiter. The intrathoracic extension in this instance was unusually large. Upon exploration through the usual cervical incision it was possible to demonstrate that there was no appreciable enlargement of the right lobe excepting for the goiter itself which was almost entirely intra-

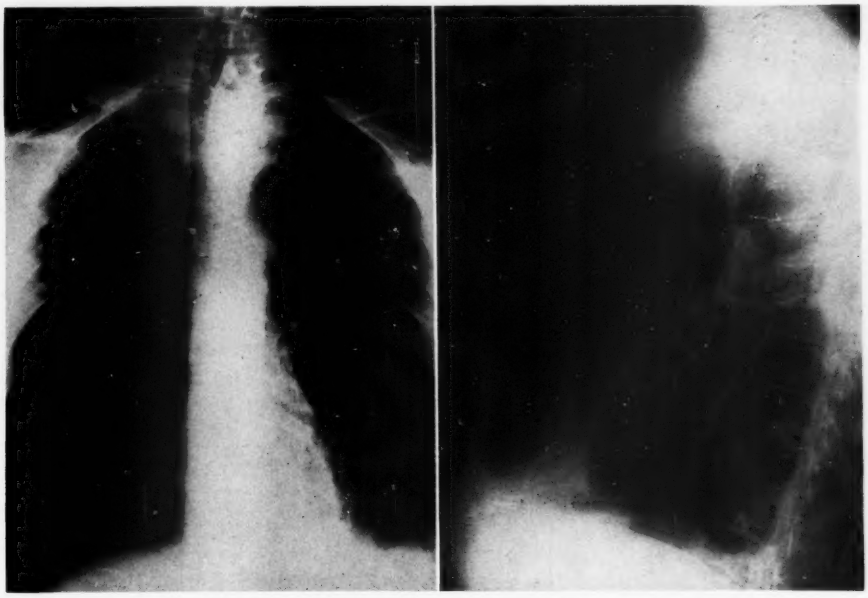

Fig. 3, left. Case 2. Anterior roentgenogram showing moderately large intrathoracic goiter with rather marked lateral displacement of trachea.

Fig. 4. Case 2. Lateral roentgenogram showing posterior location of the goiter lying upon the upper thoracic vertebrae.

thoracic. The attachment to the gland consisted only in a relatively thin and narrow strip of thyroid tissue which extended downward behind the great vessels of the neck into the posterior mediastinum where it expanded into a large goiter lying upon the anterior surface of the spine, pushing the esophagus to the left and bulging against the right pleural sac. These relations were more readily demonstrated because of the use in this case of the combined cervical and thoracic incisions (Figs. 5, 6, 7, 8).

Technical considerations. Almost without exception substernal or anterior intrathoracic goiters can be removed through the usual cervical thyroidectomy incision. This is because by pushing the great vessels and trachea posteriorly during their development they create a space from which they can be enucleated with relative ease by exerting upward traction on the gland while the dissection around and beneath the goiter is being accomplished.

Posteriorly descended goiters, on the other hand, may present a considerable obstacle to removal through the neck. This is because the space through which they must be extracted is relatively small and because when very large they are almost invariably attached only by a narrow pedicle which occupies a small space at the thoracic inlet. This space is bounded laterally by the first rib, posteriorly by the vertebral column, medially by the trachea and esophagus, and anteriorly by the carotid sheath and the subclavian and innominate vessels. Through this small, rigid-walled aperture it is impossible to extract a very large posterior goiter attached to the gland by only a narrow segment of thyroid tissue (Fig. 8). It is necessary in such cases to remove the goiter through a thoracotomy incision. The necessity for using the thoracic approach can be decided on the basis of the size of the tumor mass as visualized in roentgenograms of the chest. In Cases 5 and 6 the necessity for using the thoracic approach was obvious. As in Case 3, the decision to open the chest may have to be made after an attempted removal through

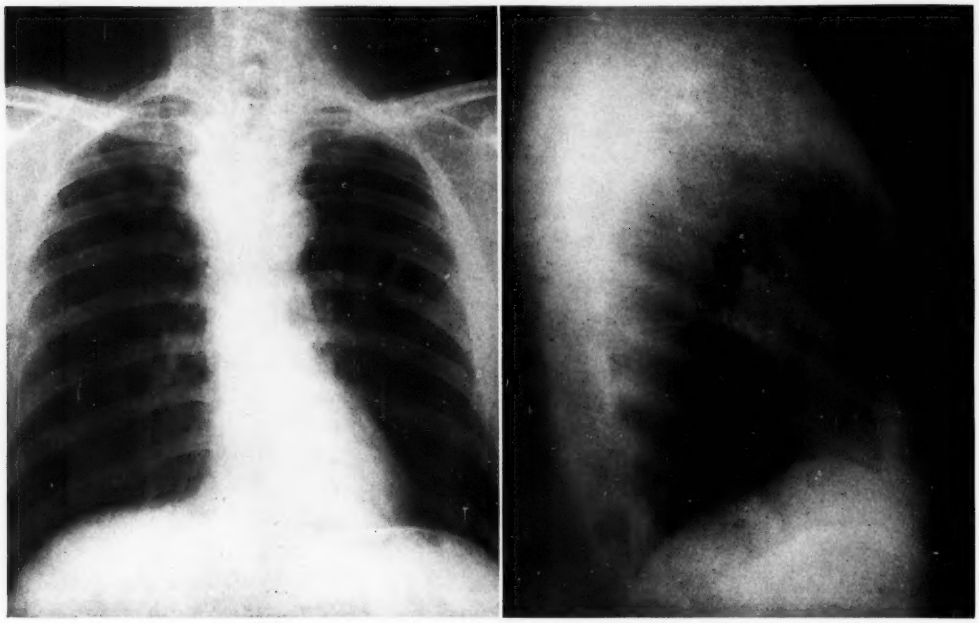

Fig. 5, left. Case 3. Anterior roentgenogram showing intrathoracic goiter bulging to the right with downward descent to approximately the level of the arch of the azygos vein.
Fig. 6. Case 3. Lateral roentgenogram showing posterior location of the goiter.

a cervical incision has failed. There is no objection in such a situation to turning the patient on his side and removing the mass through a standard thoracotomy incision provided that the anesthetist has taken the precaution to use an intratracheal tube so that positive pressure may be exerted upon the lung. Of the 6 cases reported, the thoracic approach was mandatory in 2 and preferable in 1 case. In the 3 other cases the goiter was small enough to be removed easily through the neck.

Symptoms. Five patients complained of cough; in 2 of these the cough was very troublesome. Expectoration was not a factor in any case. Two patients experienced moderate dysphagia as a result of pressure on the esophagus. In 1 there was pain referred to the shoulder on the side where the goiter was. A moderate degree of dysphonia was noticed by 1 patient. One patient experienced no symptoms whatever. The symptoms in all 5 cases in which they were present were mild, but complete relief resulted from the operation in all cases.

Indications for operation. The decision to operate in cases of posterior intrathoracic goiter should be based partly on the presence of symptoms but partly also upon the prediction that progressive difficulty is to be anticipated. An equally important factor is the knowledge that as the tumor enlarges, the technical difficulties encountered in its removal inevitably increase. If operation is performed early, an excision of the mass can be accomplished through the usual thyroidectomy incision. If the goiter exceeds a certain size, however, a thoracotomy becomes necessary for its extirpation. The desirability of early discovery and prompt removal of these tumors is therefore obvious.

CASE REPORTS

CASE 1. A. R., MGH No. 587155, female, aged 33 years, was admitted to the hospital on November 17, 1947 because of trouble with swallowing. About 18 months previously she had had an attack of acute choking after swallowing a peanut. Since that time

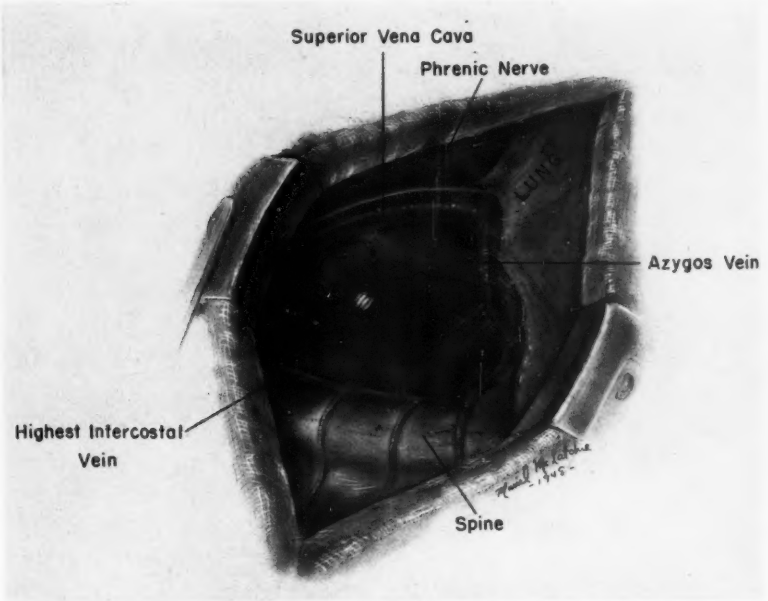

Fig. 7. Case 3. Drawing based on sketches made at operation showing the goiter through the thoracotomy incision. Note the relations of the mass to the spine, the azygos vein, and the superior vena cava.

she had had the feeling that there was a lump present behind the upper sternum inhibiting the swallowing of large particles. She had had no vomiting or bleeding. She had a dry cough which she thought was due to pressure. She had lost about 3 pounds in weight during the previous few weeks but was otherwise well. She denied nervousness, increase of appetite, insomnia, intolerance to heat, diarrhea, or any other signs of thyrotoxicosis.

On physical examination no mass could be felt in the neck. The heart was regular, the sounds of good quality, and no murmurs were heard. Blood pressure was 130/85.

Roentgenographic studies showed a mass in the right side of the neck displacing the esophagus to the left (Figs. 1 and 2). Her basal metabolic rate was +21 per cent.

An operation was performed on November 19, 1947. The usual curved thyroid incision was made. The pretracheal muscles were separated in the midline and retracted so as to expose the right lobe of the thyroid. The lobe itself appeared to be essentially normal, but arising from the posterior aspect above the lower pole there was a rounded, soft tumor mass about 4 centimeters in diameter, possibly larger, extending downward into the superior mediastinum behind the innominate artery. By getting into the proper plane of cleavage it was easy to liberate this tumor and deliver it through the wound. In doing this, however, it burst and a considerable amount of fluid was evacuated. From that point on the removal of the abnormal mass was carried out in the usual fashion. At the completion of the operation the layers were approximated with interrupted fine silk sutures. No drainage was used.

After microscopic diagnosis the pathologist reported the tumor to be nodular goiter with hyperplasia and involution. She made an uneventful recovery and was discharged from the hospital in excellent condition 5 days postoperatively with the wound well healed, swallowing well, and without evidence of hoarseness.

Case 2. H. B., MGH No. 610270, male, aged 57 years, was admitted to the hospital on March 8, 1948, because of hoarseness, cough, hemoptysis, asthmatic breathing, and fatigue. He had a prolonged history of asthma. There was some evidence of bronchiectasis on the roentgenogram of the chest, but bronchoscopic examination was completely negative. Roentgen examination, however, showed the presence of a soft tissue mass in the left upper mediastinum deviating the trachea to the right (Figs. 3 and 4). Because this mass appeared to be pressing on the trachea and was believed to be contributing to his symptoms, an operation was advised. His basal metabolic rate was −4 per cent.

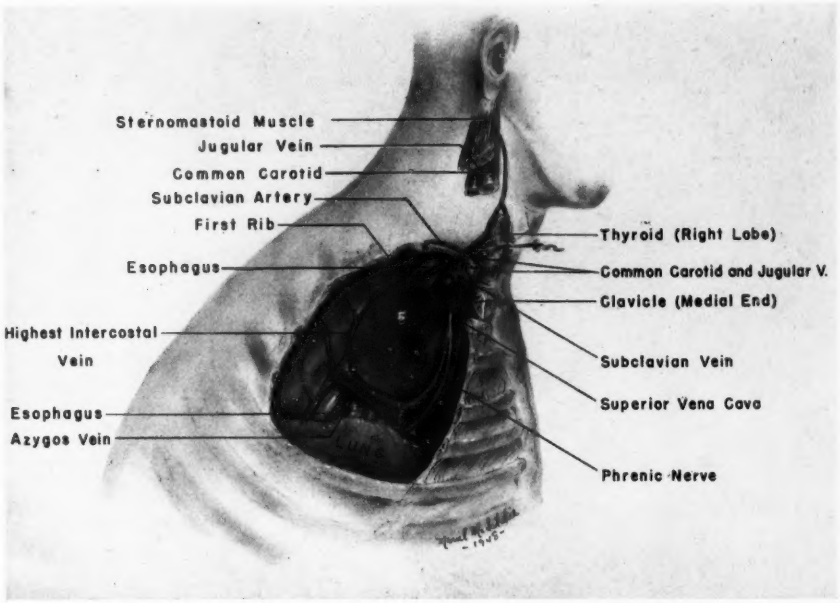

Fig. 8. Case 3. Composite drawing based upon observations of the anatomical relations of the goiter as seen through both cervical and thoracic incisions. Note: (1) The tumor arises by a narrow pedunculated attachment from the posterolateral aspect of the right lobe of the thyroid. (2) It had descended behind the vessels in the carotid sheath, the subclavian vein and artery, the innominate vein, and the superior vena cava. (3) The recurrent laryngeal nerve (not shown) approaches the larynx beneath the uninvolved lower pole of the lobe and anterior to the pedicle of the goiter.

The operation was performed on March 19, 1948. The usual thyroid incision was made. The pretracheal muscles were parted in the midline and retracted. By entering the proper plane of cleavage it was possible to palpate downward along the left lobe of the thyroid and the intrathoracic goiter was felt. The tumor arose from the posterior aspect of the thyroid lobe instead of from the inferior pole. It extended behind the carotid sheath posteriorly and lay against the anterior surface of the vertebral column. There were no adhesions so that it was relatively easy to pull it up by grasping it with tenaculum forceps. It was then delivered through the wound and removed, except for a small portion of the lobe which was left behind. The cut edges of the lobe were approximated by means of several fine silk sutures after the vessels were tied. The muscles were then drawn together, the divided platysma edges were sutured, and the skin was closed with silk. No drainage was used.

On pathological examination a microscopic diagnosis of struma nodosa micro et macro folliculare was made.

The patient's postoperative recovery was uneventful and he was discharged from the hospital in good condition.

CASE 3. W. K., MGH No. 602786, male, aged 43 years, was admitted to the hospital originally for diagnosis and treatment of a very troublesome diarrhea. Roentgen-ray examination of the chest revealed the presence of a rounded mass in the upper mediastinum on the right side, displacing the trachea to the left (Figs. 5 and 6). The esophagus was not much deviated. There was slight motion of the mass on swallowing. There were no symptoms attributable to this tumor, but excision was advised on the basis that it should be removed before it became large enough to cause serious trouble. His basal metabolic rate just prior to operation was +4 per cent.

An operation was performed on March 24, 1948. The usual thyroid incision was made in the neck. The pretracheal muscles were parted in the midline and retracted. It was soon discovered that there was a mass extending downward from the posterior surface of the right lobe of the thyroid behind the jugular vein and carotid artery and descending into the thorax posteriorly so as to lie upon the vertebral column. A tenaculum was applied and considerable force was exerted in an effort to pull the tumor up. Blunt dissection with the finger down into the chest as far as could be reached failed to free the mass and it seemed obvious that it could not be delivered

Fig. 9, left. Case 4. Anterior roentgenogram showing posterior intrathoracic goiter of fairly large size removed through a cervical incision.

Fig. 10, Case 4. Lateral roentgenogram showing posterior location of the goiter with marked anterior deviation of the trachea.

readily through the neck. The cervical incision was therefore closed and the patient was turned on his left side.

A standard thoracotomy incision was made on the right side and the chest was opened through the fourth intercostal space. The large bulging goiter could be seen protruding beneath the mediastinal pleura (Fig. 7). It extended downward as far as the azygos vein. It pushed the superior vena cava forward and was resting upon the vertebral column. An incision was made in the mediastinal pleura and the goiter was freed of its local fixation, which was quite considerable. In the process of dissection it broke with the discharge of 1 or 2 ounces of watery fluid. An effort was made to get around the proximal attachment of the goiter in order to remove it from below, but it was discovered that there was a medial extension in the region of the trachea and esophagus which could not be reached because it was so high in the neck. On the other hand, the reduction in the size of the tumor and the freeing of its adhesions made it possible to withdraw it from the chest through the neck. It was therefore decided to close the chest wound and to remove the goiter through the cervical incision.

After closure of the thoracotomy incision the patient was put on his back once more. The cervical incision was reopened and the goiter was delivered with relative ease. It had arisen from the posterior aspect of the gland and not from the inferior pole. It was necessary, however, to remove the major portion of the right lobe in order to get the base of this goiter out. This was done without much difficulty and the wound was once more closed in layers, by means of interrupted silk sutures without drainage.

On microscopic examination the pathologist made a diagnosis of nontoxic nodular goiter, involution, hyperinvolution with cyst formation, and adenoma.

Following operation the patient had periods of slight difficulty with breathing, but his recovery was essentially uneventful and he was discharged from the hospital in excellent condition.

Case 4. I. E., MGH No. 600308, female, aged 56 years, was admitted to the hospital on December 4, 1947. Nine months previously she had had the rapid onset of paroxysms of coughing. There was no loss of weight. Her local doctor had discovered the presence of a superior mediastinal tumor which was treated by roentgen therapy with very slight shrinking in size. There was no dysphagia, feeling of pressure, pain, or hemoptysis.

Roentgenographic studies of the chest showed a smooth, rounded tumor mass in the superior mediastinum bulging slightly more to the right than to the

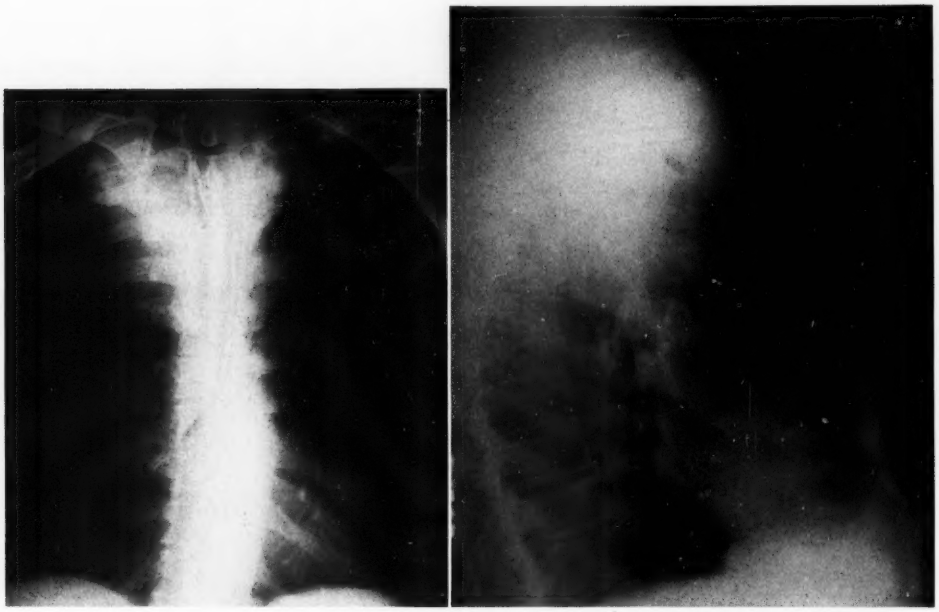

Fig. 11, left. Case 5. Anterior roentgenogram showing unusually large posterior intrathoracic goiter coming from right lobe of thyroid, removed through a thoracotomy incision. Deviation of esophagus shown.

Fig. 12. Case 5. Lateral roentgenogram showing posterior location of the tumor actually overlying the side of the vertebral column.

left, displacing the esophagus and trachea anteriorly and to the right (Figs. 9 and 10). The mass showed slight pulsation which appeared to be transmitted. It moved upward on swallowing. No calcification was seen within the mass and there was no evidence of bone erosion. Both lung fields were clear.

On December 8, 1947, an operation was performed. Under intratracheal anesthesia the neck was opened through a collar incision. The pretracheal muscles were parted in the midline and divided, so that the thyroid was exposed. The thyroid was seen to be generally enlarged, more on the right, and extending downward from the right lobe was a large intrathoracic extension which was responsible for the shadows seen in the roentgenogram. This was delivered out of the chest without undue bleeding and a right subtotal thyroidectomy was performed. The isthmus was then removed. The left lobe was exposed and a partial thyroidectomy was done on the left side. The superior pole vessels were secured with interrupted silk bilaterally. The inferior branch of the inferior thyroid artery was taken in the substance of gland. Wound was closed without drainage.

The pathologic diagnosis on microscopic examination was nontoxic nodular goiter; involution.

The patient withstood the operative procedure well and made a good recovery. She was discharged from the hospital in good condition.

Case 5. A. A., MGH No. 402519, male, aged 63 years, was admitted to the hospital on April 29, 1943 complaining of pain and weakness of the right arm of 10 months' duration. Four months previously a roentgen examination had revealed the presence of a mass in the right upper chest. This was treated by roentgen-ray in another hospital without decrease in size. During the month preceding admission he had had deep soreness in the right side of the neck. He had had a cough which disappeared following the roentgen-ray treatment. There had been no weakness, no weight loss, no anorexia, and no hemoptysis. He had noticed no change in his voice, no dyspnea, orthopnea, or giddiness.

Physical examination showed the trachea to be deviated to the right, but there were no masses or glands palpable. There was deep tenderness in the posterior triangle and in the posterior base of the neck.

Roentgenograms showed a smooth, rounded, homogeneous mass arising from the upper mediastinum and lying between the trachea and the esophagus (Figs. 11 and 12). The mass measured approximately 13 by 13 centimeters. It was largely on the right side, but there was apparent extension to the left side. It was attached to the trachea and displaced it to the left. There was no pulsation. It appeared to change in shape on deep inspiration and to vary slightly on changing the position of the patient.

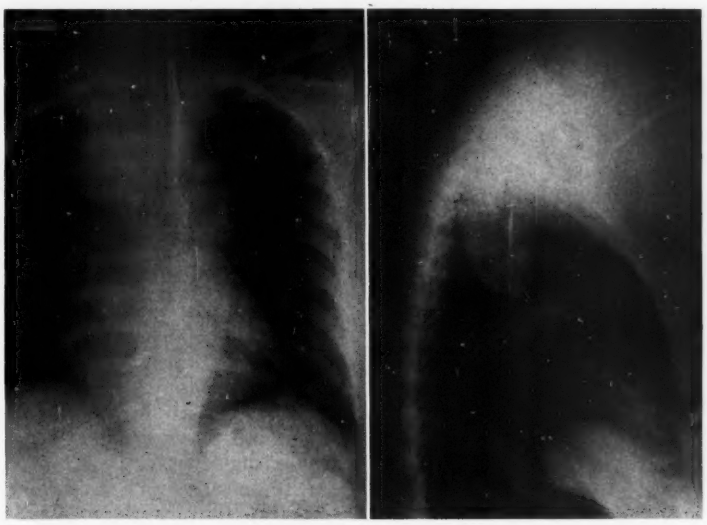

Fig. 13, left. Case 6. Anterior roentgenogram showing very large posterior intrathoracic goiter arising from right lobe of thyroid, removed through thoracotomy incision.

Fig. 14. Case 6. Lateral roentgenogram showing posterior location of goiter overlying the side of the vertebral column.

An operation was performed on May 3, 1943. A long oblique incision was made across the right chest. The chest was opened by the rib resection technique through the bed of the sixth rib. The tumor appeared to be mediastinal in origin, but it protruded a long distance into the right side of the chest, extending posteriorly as it went. There were no adhesions of the lung. The mediastinal pleura was incised, and the tumor was found to be covered by a network of very large, thin-walled veins. It had a pedicle coming from the base of the neck. After the periphery of the tumor was freed the pedicle was reduced to about 2 by 3 centimeters in size and this tissue felt exactly like thyroid tissue. The tumor was obviously solid. It was immediately apparent that the growth had arisen from the right lobe of the thyroid gland, extending down lateral to the trachea in the chest and behind the subclavian artery.

Clamps were placed on the pedicle and the tumor was removed. The vessels of the pedicle were secured with suture ligatures. The incision in the mediastinal pleura was closed with interrupted silk sutures and the lung was re-expanded. The chest wall was closed in the usual manner by means of silk sutures. No drainage was used.

The pathologic diagnosis after microscopic examination was mediastinal thyroid; hyperinvolution.

On the first postoperative day 700 cubic centimeters of air was aspirated from the right pleural space. On the next day he had a period of auricular fibrillation, but this was readily controlled by means of cedilanid. On the fourth day aspiration of the chest yielded 500 cubic centimeters of deeply blood-stained fluid. His subsequent convalescence was slow but satisfactory and he was discharged from the hospital in good condition and relieved of his symptoms on the nineteenth day following operation.

Case 6. K. C., PMH No. 47: 374, female, aged 51 years, was admitted to the hospital on March 3, 1947. Roentgen-ray examination during a routine chest survey of all the employees of the company with which she was associated had revealed the presence of an upper thoracic mass. Up to that time she had thought she had no symptoms, but on careful questioning it was quite apparent that she had had in the previous year or two an increasing amount of dry irritative cough and more recently a certain amount of dysphagia.

Physical examination was negative except for possibly a little more dullness in the superior mediastinum than one might expect. Roentgen-ray examination, however, revealed the presence of a smoothly rounded mass in the right upper thorax medially and anteriorly (Figs. 13 and 14). The mass measured about 6 by 8 centimeters and was of homogeneous density. By fluoroscopy it showed no evidence of pulsation, but there was a definite tracheal tug with swallowing. The heart and great vessels appeared normal, and examination of the esophagus showed no abnormality. The mass was in contact with the trachea and produced very slight narrowing and displacement of it.

An operation was performed on March 6, 1947. A long oblique incision was made across the right chest and the fourth rib was resected. This incision gave good exposure to the superior portion of the chest and the superior mediastinum. The tumor was very large, extending from the base of the neck down to the right main bronchus. Its lower end depressed the arch of the azygos vein. It lay in the posterior aspect of the chest behind the level of the superior vena cava and did not come at all close to the anterior chest wall. It was obviously a posteriorly placed intrathoracic goiter. It was very vascular, but when the proper plane of cleavage was entered, it was readily dissected free. It was necessary, in order to start the dissection in the proper plane, to divide the azygos vein. The tumor was freed and the large vascular pedicle coming down from the right lobe of the thyroid beneath the clavicle and first rib was secured by means of hemostats and stitch ligatures of heavy silk. In doing this the subclavian artery and vein had to be carefully avoided. No evidence of the recurrent laryngeal nerve could be made out.

After the tumor had been removed and the vascular bleeding points had been secured, the edges of the mediastinal pleura were approximated with interrupted silk, the lung was fully expanded, and the chest wall was closed in layers, the silk technique being used.

On microscopic examination the pathologist reported this tumor to be multiple colloid adenomatous goiter.

The postoperative convalescence was uneventful. The wound healed well and she was discharged from the hospital in excellent condition on the seventeenth postoperative day.

CONCLUSIONS

1. In general, intrathoracic goiters should be removed not only because of the symptoms they may be causing when the patient is first seen, but also because as they increase in size the technical difficulty of the operation becomes greater.

2. In order to plan the operation to the best advantage it is important for the surgeon to distinguish between the anterior substernal goiters and those which lie posteriorly. The former can almost invariably be removed through a cervical incision. The latter, on the other hand, may require a thoracotomy if they are unusually large.

3. The suggestion that the descent of a goiter into the posterior mediastinum is caused by the fact that it happens to arise from the posterior or lateral aspects of the thyroid lobe above the lower pole appears to be a reasonable explanation of this relatively infrequent occurrence.

OUTLET PELVIMETRY

Results in Measuring the Symphysis-Biparietal and Sacral-Biparietal Diameters in 145 Primiparous Women

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THE use of manual methods to determine the size and contours of the bony pelvic outlet is an important obstetrical procedure. The simple palpation of the arch, the tubera ischii, and the coccyx and lower sacrum, even without mensuration, will give to the experienced examiner valuable information. Unfortunately, because of the lack of definite end-points, such as are found in the pelvic inlet and the pelvic midplane, the dimensions of the outlet in terms of diameters are subject to variation due to subjective interpretation. This is true in both the manual and the roentgenologic methods used for this purpose. Having these considerations in mind, the senior author described in 1946(3) a pelvimeter for estimating the symphysis and sacral biparietal distances. From the mechanics of head and outlet relationship it is recognized that the width of the subpubic angle and the shape of the pubic arch are of considerable importance, but, as Allen logically states, "The important point is clearly how close the occiput is allowed to approach the lower edge of the symphysis." Therefore, as an alternative to attempting to determine the subpubic angle and a transverse outlet diameter, the measurement of the symphysis-biparietal distance is recommended. This is the distance within which a normal biparietal diameter cannot approach the lower edge of the symphysis. This distance, as well as the sacral-biparietal distance, can be determined externally by the pelvimeter described previously (3, Fig. 7). The crossbar of this instrument is 9 centimeters and, allowing about 0.5 centimeter for the thickness of the soft parts covering the pubic rami in their medial aspect, represents an average biparietal diameter of 9.5 centimeters, a figure close to the average of 93 millimeters given by Scammon and Calkins. When this instrument is used the patient is brought well down over edge of the examining table in the lithotomy position; the arch is thoroughly palpated, by using both hands simultaneously as in the manner usually described in textbooks. The course of the rami downward is noted, whether straight or moderately or widely arcuate. The crossbar of the pelvimeter is then passed between the rami and by upward pressure it is brought as near the symphysis as possible. As the crossbar is held in this position, the end of the arm of the pelvimeter is brought to the lower edge of the symphysis and the symphysis-biparietal distance read on the scale. With the crossbar in position the tip of the arm of the pelvimeter is swung posteriorly to rest externally over the tip of the sacrum. The sacral-biparietal distance is then determined from the scale after subtracting 1 centimeter, which represents the thickness of the sacrum.

The 145 women included in this discussion, all primiparas who had been followed in labor, had a roentgen pelvimetric survey of the pelvis according to the Thoms and Wilson (4) technique, which consists of an inlet and lateral film from which the important diameters of the inlet and pelvic midplane may be measured.

The values for the symphysis-biparietal and sacral-biparietal diameters in these women have been determined and the relationship of these measurements to the type of pelvis, to the transverse diameter of the midplane, and to the type of delivery has been noted. For purposes of clarification the pelvic classification which we have found of practical value is reviewed, namely:

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I. Dolichopellic type—The transverse diameter of the inlet is less than the anteroposterior diameter.
II. Mesatipellic type—The transverse diameter of the inlet is greater than the anteroposterior diameter by no more than 1 centimeter.
III. Brachypellic type—The transverse diameter of the inlet is from 1.0 to 2.9 centimeters greater than the anteroposterior diameter.
IV. Platypellic type[1]—The transverse diameter of the inlet is 3 centimeters or more greater than the anteroposterior diameter.

In considering the pelvic arch in relation to the type of pelvis, it would be expected that the dolichopellic type, with its relatively narrowed sidewalls, also would present a relative narrowing of the arch and, therefore, relatively longer symphysis-biparietal and sacral-biparietal diameters. Conversely the brachypellic type would show relatively shorter symphysis-biparietal and sacral-biparietal distances. These diameters in the mesatipellic type should occupy a midposition. These expectations were borne out:

	Average diameter centimeters
Dolichopellic group—45 pelves	
Symphysis-biparietal diameter	5.0
Sacral-biparietal diameter	8.0
Transverse midplane diameter	9.9
Mesatipellic group—55 pelves	
Symphysis-biparietal diameter	4.5
Sacral-biparietal diameter	7.7
Transverse midplane diameter	10.3
Brachypellic group—45 pelves	
Symphysis-biparietal diameter	4.9
Sacral-biparietal diameter	7.6
Transverse midplane diameter	11.0

A further correlation of the narrowing of the pelvic sidewalls, to the pelvic arch is shown by the relationship of the transverse midplane diameter to the symphysis-biparietal diameter in Table I.

TABLE I.—AVERAGE TRANSVERSE MIDPLANE DIAMETER FOR DIFFERENT SYMPHYSIS-BIPARIETAL DIAMETERS

Number of cases	Symphysis biparietal	Average transverse midplane
3	2.5	11.1
10	3.0	11.0
2	3.5	10.8
28	4.0	10.4
12	4.5	10.6
58	5.0	10.6
15	5.5	10.4
13	6.0	10.5
1	6.5	9.9
4	7.0	9.5

OPERATIVE INTERFERENCE

With transverse narrowing of the lower pelvis both in midplane and outlet as evidenced by a relatively increased symphysis-biparietal distance, an increased incidence of operative intervention might be expected. This is shown in the type of delivery of these 145 women. We recognize, however, that the indications for operative delivery in primiparas, which includes low forceps, are manifold. Our results show that of these 145 primiparas, in 113 with a symphysis biparietal distance of 5.0 centimeters or less, 44, or 38.9 per cent, were delivered by operation. In 32 women with symphysis-biparietal diameter greater than 5.0 centimeters, 17, or 53.1 per cent, were delivered by operation.

From this study of outlet pelvimetry in relation to the fetal biparietal diameter certain conclusions previously held have become reinforced. The chief of these is that, in order to evaluate pelvic capacity, the pelvis must be studied as a whole; that is, inlet, midplane, and outlet measurements must be included. It is probable that outlet constriction rarely exists alone but is accompanied by relative constriction somewhat higher in the pelvis, especially in the midplane. A proper pelvic survey should include roentgen pelvimetry with inlet and lateral views showing pelvic contours and from which dimensions can be measured. Manual palpation of the pubic arch with measurement of the symphysis-biparietal and sacral-biparietal diameters, as outlined here, are useful adjuncts to roentgen pelvimetric procedures.

[1] The platypellic type is relatively infrequent and almost always shows changes characteristic of pelvic rickets. In the present group there were no pelves of this type.

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THE BIOLOGICAL CHEMISTRY OF WOUND HEALING

II. The Effect of dl-Methionine on the Healing of Surface Wounds

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In a previous publication (5) two of the authors showed that the parenteral administration of dl-methionine to protein-depleted rats shifts the curve of wound healing of abdominal wounds toward normal. In that study the healing of the skin was excluded from the experiments.

Healing of peritoneum, muscle, and fascia is primarily a process of fibroplasia. The healing of a surface defect is primarily a process of contraction and epithelization (2, 3). It seemed to us to be of interest to record the effect of dl-methionine on the healing of surface wounds in protein-depleted rats, and to record briefly observations on 2 patients.

MATERIAL

Young white adult male rats of pure Wistar strain, purchased from a commercial breeder, were used in the experiments. The first group consisted of 45 normal control animals. The second group of 23 animals were depleted and rendered hypoproteinemic by means of diet. The third group of 16 animals were depleted and then received dl-methionine. The fourth group of 16 animals were normal controls which received dl-methionine.

METHODS

Under ether anesthesia and using a template, a standard sized area of skin ($r = 1$ cm. $a = 3.14$ sq.cm.) was excised from the freshly shaven back of the animals. The wounds were traced on cellophane at 4 day intervals. The cellophane image of the wounds was transferred to bond paper and the bond paper weighed on an analytic balance. The weight of the bond paper per square millimeter was previously determined and by a simple factor weight was translated to size. This gravimetric method of Douglas (4) is far more simple and rapid than the planimeter, and it was found to be satisfactory.

Group 1, normal control animals, were maintained on a basal ration of purina chow pellets, preoperatively and postoperatively.

The animals in Groups 2 and 3 were placed on a diet containing 0.23 per cent nitrogen and consisting of 10 per cent carrot powder, 5 per cent crisco, 3 per cent agar, 1 per cent salt, and 81 per cent moisture. This diet, used in previous studies (5), was found uniformly to render an animal hypoproteinemic within 5 weeks. At the expiration of 5 weeks the animals were operated upon and their wounds measured as those in Group 1. Postoperatively, the animals of Groups 2 and 3 were maintained upon the nitrogen-poor depleting diet. However, the animals in Group 3 received 150 milligrams of dl-methionine subcutaneously daily during the entire postoperative period of observation.

The fourth group of animals were normal animals which received 150 milligrams of dl-methionine parenterally, starting on the first postoperative day and continuing throughout the period of observation. The animals were maintained on a diet of purina chow pellets.

At the completion of the experiments in Groups 1, 2, and 3, heart blood was obtained for total protein determinations.

RESULTS

The results are tabulated in Table I, and shown graphically in Figures 1, 2, 3.

The normal control rats gained an average of 56 grams during the experiment, had a normal blood protein of 6.5 grams per cent and healed in 27.1 days.

The depleted rats lost 106 grams, had 3.9 grams per cent of protein in the blood and

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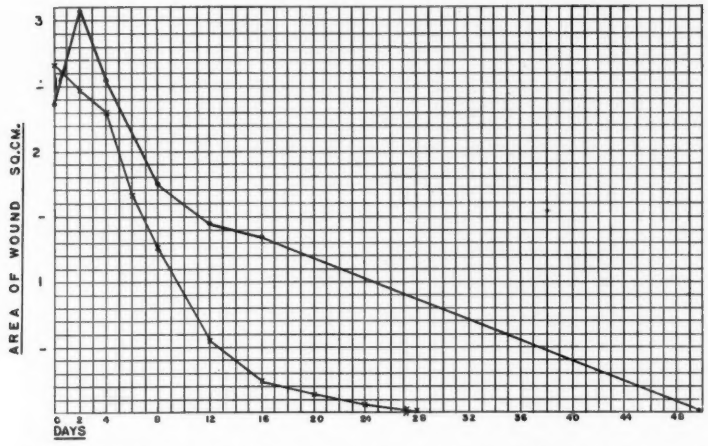

Fig. 1. Comparison of healing of surface wounds in normal control (x——x——x) and in hypoproteinemic (•——• — •) animals.

healed in a calculated average time of 49.8 days. Actually only 6 of the 23 animals in this group went to the stage of final healing. The others died unhealed. In order to obtain data for mathematical comparison, the healing time of the 17 unhealed animals was calculated by estimating the day of healing according to the normal healing curve and not the healing curve of a protein-depleted animal. Had we used the latter calculation, the average healing time would have exceeded by far the 49.8 days recorded. Clinically, the wounds appeared pallid, or, as Thompson, Ravdin, and Frank expressed it, "they appeared as if a local anesthetic had been injected in the tissues."

TABLE I.—SUMMARY OF HEALING OF SURFACE WOUNDS IN RATS

Group No.		No. animals	Wt. start grams	Wt. end grams	Change grams	Bl. prot. gm. percent	No. healing days	Skin diameter sq. cm.
1	Normal controls	45	222	278	+56	6.5	27.1	7.8
2	Hypoproteinemic	23	206	100	−106	3.9	49.8	20.5
3	Hypoproteinemic plus 150 mgm. methionine	16	219	136	−83	4.0	32.6	6.3
4	Normal plus 150 mgm. methionine	16					31.6	5.1
5	Calculated by Du Nouy's equation						31.75	

The protein-depleted rats that received dl-methionine lost an average of 83 grams, the blood proteins averaged 4.0 grams per cent and the wounds healed in 32.6 days. In all of these animals wound healing occurred. In the normal animals that received dl-methionine healing took place in 31.6 days. The healing time of a rat wound the size of our average wounds as calculated by Du Nouy's equation for the healing of surface wounds, is 31.75 days.

Except for the untreated protein-depleted hypoproteinemic group, statistically each series was well grouped as regards healing time, as indicated by the standard deviation from the mean.

DISCUSSION

As expected from clinical observation and from previously published work, the healing time of a surface wound in a protein-depleted animal is prolonged. The healing of surface wounds in protein-depleted animals that received dl-methionine approaches the normal, notwithstanding the fact that the animals were maintained upon a depleting diet and remained depleted according to the level of the

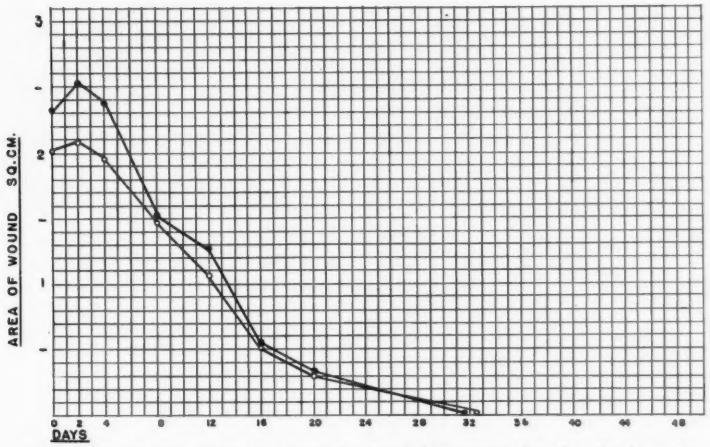

Fig. 2. Comparison of healing of surface wounds in hypoproteinemic animals receiving dl-methionine (o——o——o) and normal animals receiving dl-methionine (•——•——•).

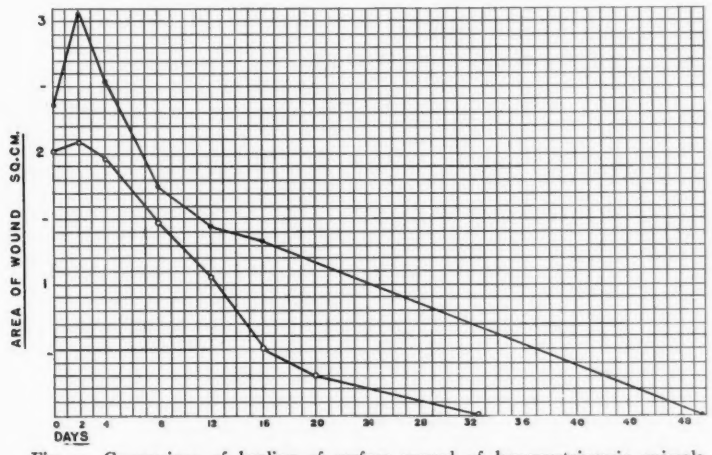

Fig. 3. Comparison of healing of surface wound of hypoproteinemic animals (•——•——•) and of hypoproteinemic animals receiving dl-methionine (o——o——o).

blood proteins. These results also follow those previously recorded for abdominal wounds.

Localio, Morgan, and Hinton outlined an hypothesis indicating that these results may be due to the fact that dl-methionine supplies necessary sulfydryl (SH) radicals to the enzymatic activity of the chemical reactions that lead to healing. The present study does not prove that hypothesis. However, it does indicate that abnormal healing in a structure containing concentrations of sulfur (hair and skin) can be corrected in large part by an essential sulfur-containing amino acid.

It is of some importance to emphasize that dl-methionine did not speed the healing of a normal wound. These surface wound experiments are more easily put to test in the human than the experiments on the abdominal wall. We have observed 2 patients whose histories we wish to record briefly.

Fig. 4, left. Case 1. Patient prior to treatment with dl-methionine.

Fig. 5. Case 1. Patient 6 months after treatment with dl-methionine.

CASE 1. F. A., Age 10 years, sustained extensive third degree burns 2½ years prior to our observation. For 1 year at another hospital, several attempts to cover the granulations with skin grafts not only failed but the donor sites failed to heal. During the next year at the New York Post-Graduate Medical School and Hospital, 16 attempted skin grafts failed despite antibiotics, transfusions, plasma, oral and intravenous hydrolysates, and numerous forms of local preparation of recipient area. The blood proteins ranged from 5.6 to 5.8 with a normal albumin globulin ratio. The hemoglobin and red blood cell count were maintained within normal limits, and the hematocrit ranged between 41 and 43. When we were asked to see the patient his weight was 43 pounds.

The patient was placed on 1 gram of dl-methionine 3 times daily for 2 weeks with little observable result. At the same time, furacin was used as a local dressing. The dose of dl-methionine was then raised to 2 grams 3 times daily, and on the ninth day, epithelization for the first time was observed in the wound edges. Therapy was continued for 14 weeks, during which time many of the areas epithelized spontaneously. Three skin grafts were attempted and all remained viable.

Six months later the patient weighed 83 pounds. Wounds were healed. Blood protein was 6.7 grams (Figs. 4 and 5).

CASE 2. Male, aged 77 years, entered the Fourth Surgical Division of Bellevue Hospital complaining of chronic ulcers of both ankles of 7 years' duration. This patient had generalized atherosclerosis and moderately severe varicosities of the lower extremities. For 16 weeks he was treated by rest, elevation, and numerous varieties of local dressings. Two separate attempts at pinch grafting of the ulcers failed. When we were asked to see the patient, the ulcer on the right covered an area of 108 square centimeters. The anterior surface of the tibia was exposed and necrotic. The ulcer on the left measured 57 square centimeters. The Achilles tendon was exposed and sloughing. Both ulcers had areas of necrotic muscle and slough at their base. The red blood count was 4.0 million, hemoglobin 12.5 grams. Blood proteins were 5.9 total; albumin 3.8; globulin 2.1. The patient was given 500 cubic centimeters of whole blood and 2,500 cubic centimeters of blood plasma. He was maintained on the general ward diet. Ten days later he was placed on 4 grams of dl-methionine 3 times daily. One week following inception of this therapy, epithelization began at the edge of the ulcers. Because of the huge size of the ulcer on the right it was decided to pinch graft this area. In an isolated area below the ankle, roughly 15 per cent of the grafted area, all grafts failed, elsewhere all grafts remained viable and spread. Ten weeks after inception of therapy the unhealed areas measured 12 square centimeters. This included only an area of exposed necrotic bone and the area below the ankle mentioned. In this latter area, epithelization was proceeding from the borders.

The ulcer on the left was not grafted. It was decided to see if this ulcer could be made to heal by epithelization. Ten weeks after inception of dl-methionine therapy, this ulcer measured 15 square centimeters. Of this, 5 square centimeters was over necrotic Achilles tendon. The patient is still under observation.

We do not offer dl-methionine as a panacea for the healing of stubborn surface wounds. Wound healing is much too complex a process to hope that any one factor will solve its problems. On the basis of our animal experiments and 2 cases, we believe that this easily tolerated, apparently nontoxic amino acid, is worthy of further controlled clinical study.

CONCLUSIONS

1. Protein depletion markedly prolongs the healing of surface wounds in rats.

2. The administration of dl-methionine in spite of continued protein depletion, restores the healing time toward normal.

3. Dl-methionine does not speed the healing of surface wounds of normal rats.

4. Two clinical cases are presented which

indicate that dl-methionine may be worthy of trial in stubborn unhealed surface wounds in protein-depleted humans.

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THE PHYSIOLOGICAL EFFECTS OF CURARE

Its Failure to Pass the Placental Membrane or Inhibit Uterine Contractions

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THE present study was undertaken in an effort to add to our knowledge of the pharmacology of curare and to establish an experimental basis for its use for operative deliveries should the need arise.

Several authors have reported the use of curare for cesarean section. Whitacre and Fisher (8, 9) reported a series of 285 cases of cesarean sections in which curare was used. The drug was given "until there was evidence of respiratory depression." One hundred units of intocostrin was the average dose. They reported that there was no depression of respiration in the baby. Cullen said, "The effect of intocostrin on the uterus has not been thoroughly studied. A number of patients have been given curare for the purpose of producing abdominal muscle relaxation during cesarean section without any apparent adverse effect on uterus or infant." In 1947, G. F. V. Anson advised the use of curare for poor risk patients "including toxemias of pregnancy, ectopic pregnancy, puerperal hemorrhage, inversion of the uterus." He made no mention of the condition of the babies. Later in 1947, T. Cecil Gray reported the use of d-tubocurarine in 30 cases of cesarean section. Premedication consisted of 1/100 grain of atropine. Fifteen units of d-tubocurarine (a subapneic dose) were injected intravenously, followed by 0.3 gram of a thiobarbiturate, "kemithal." Anesthesia was maintained with cyclopropane in a closed system. Respirations were "aided" to prevent hypoxia. He reported that the babies were awake and showed no signs of curarization, the uteri contracted normally and vigorously, retching and vomiting were rare, and the patients were awake at the end of the operation.

At the University of California Hospital we have had no reason as yet to use curare in deliveries of any type. No muscular relaxation should be needed for a classical cesarean section; instrumental deliveries from below are more easily handled by simpler anesthetic techniques. However, we believe that the use of curare might be advantageous in certain situations, such as emergency intra-abdominal or intrathoracic surgery in which the delivery of the baby is to be performed at the same time, extraperitoneal cesarean section, and perhaps mid and low forceps deliveries in which relaxation of the perineum with preservation of normal uterine tone would be of help. At this institution curare is used in doses which are calculated to produce apnea (4, 5, 6, 7). There is no evidence as to what effect such large doses would have on the fetus or the uterine muscle. Therefore, we have investigated the effect of apneic doses of curare on pregnant dogs. Although our series is small, the results in all cases are identical. For this

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TABLE I.—SUMMARY OF RESULTS

Dog No.	Total dose of curare (intocostrin) units	Duration of apnea hrs.	Duration of apnea min.	Condition of pups	Condition of uterine muscle	Condition of dog during surgery	Postoperative condition	Remarks
1	60	3	35	Breathing and squirming	Contracted normally	Good	Good	One pup given 0/2 c.c. intocostrin i.v. became limp and apneic; died after 1 hour.
2	90	2	10	Breathing and squirming	Contracted normally	Good	Good	
3	40	2	10	Breathing and squirming	Contracted normally	Good	Good	
4	40	1	45	Breathing and squirming	Contracted normally	Good	Good	
5	80	1	25	Breathing and squirming	Contracted normally	Good	Good	
6	60	2		Breathing and squirming	Contracted normally	Good	Good	
7	60	3	25	Breathing and squirming	Contracted normally	Went into shock	Good	Shock successfully treated by i.v. dextrose.
8	100	3	30	Breathing and squirming	Contracted normally	Good	Good	
9	120	4	50	Breathing and squirming	Contracted normally	Good	Good	
10	80	2	50	Breathing and squirming	Contracted normally	Good	Good	

reason we feel justified in reporting them at this time.

Ten pregnant bitches near term were used. Nine of them were premedicated with atropine 0.0006 (gr. 1/100); the tenth, due to oversight, was unmedicated. Thirty to 80 units of intocostrin (a dose calculated to produce apnea depending on the size of the dog) were injected intravenously. As soon as relaxation and apnea occurred an orotracheal tube was inserted and attached to a breathing bag and a cylinder of oxygen. "Controlled respiration" with oxygen was instituted and continued throughout the procedure. If the dog began to make respiratory efforts before the puppies were delivered, a subsequent dose of 10 to 40 units of intocostrin was given. An abdominal wall block with 1 per cent procaine with epinephrine was done as soon as the endotracheal tube was inserted, and cesarean section performed. Care was taken that the dogs were completely curarized, limp, and apneic until all the puppies were delivered. Controlled respiration was continued until the curare had worn off and the dog was breathing well with both intercostal muscles and diaphragm.

In all 10 cases the results were identical. As soon as the mother's abdominal wall relaxed it became apparent that the pups were not curarized; their intrauterine squirming became so evident that it seemed as if they would break out of the abdomen by their own efforts. On delivery every one of them (69 in all) breathed, squirmed, and in every way behaved like normal pups, this in spite of the fact that in more than half the cases they were considerably premature. None of them was kept alive for more than 2 months, due to lack of facilities in the animal house, but in no case was there any evidence that their death was caused by the curare the mother had received. In every case the uterus contracted normally, with or without the use of ergotrate. In all cases the mothers made uncomplicated recoveries.

The possibility that lack of curarization of the pups might be due to resistance to curare rather than to absence of placental transmission of curare was considered. Four units of intocostrin were injected into the umbilical vein of a lively, breathing pup while it was still attached to the placenta, causing complete apnea in 15 seconds. The pup could not be intubated because of the minute size of the larynx and artificial respiration by squeezing the chest was carried on for about an hour. After 45 minutes a few diaphragmatic contractions were felt, but a little later the heart

stopped. It is probable that our attempts at resuscitation were too rough.

Table I gives a summary of our results.

Although we hesitate to report an isolated case, the results in this instance parallel so exactly the findings in dogs that we believe they should be included.

A hysterotomy and sterilization with curare-nitrous oxide anesthesia were performed on a 19 year old epileptic girl, 4½ months pregnant. A single dose of 200 units of curare was administered 5 minutes after the nitrous oxide anesthesia was begun. The baby was delivered 40 minutes after the administration of curare, and when the patient had been in apnea for 35 minutes. The baby was too small to make any respiratory efforts, but all its normal reflexes (withdrawal, knee jerks, etc.) were present and as active as could be expected in a normal fetus of that size. The mother's uterine muscle contracted perfectly normally. The duration of the operation was 1 hour 40 minutes; the duration of apnea, 1 hour 5 minutes. The baby, of course, was not viable, but the mother made a normal recovery.

CONCLUSIONS

1. Curare in apneic doses in dogs does not pass the placental membrane nor inhibit normal postpartum uterine contractions.

2. The reports of previous workers and our own limited observations lead us to believe that these findings can be applied to human patients.

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OBSERVATIONS ON THE MACROCYTIC ANEMIA ASSOCIATED WITH PREGNANCY

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FOR many years we have been studying nutritive failure in families living in areas in which undernutrition is endemic. We have observed in this large group that many persons develop an anemia secondary to infection or hemorrhage, but it is not with this type of anemia that we are concerned in this paper. This report is concerned strictly with the anemia of nutritional origin. The longer we study nutritional anemia, the more it appears to us that it is always a symptom and that in every instance it is indicated that the cause must be found and eliminated as well as the anemia treated specifically.

The relationship of anemia in the mother and the young infant is close, closer perhaps than has been realized. For a number of years we have been studying the anemia complicating pregnancy, which some call the pernicious anemia of pregnancy. It is a macrocytic anemia with a high color index and it responds to liver, folic acid, or yeast. If the mother is not treated while pregnant, the infant also may have anemia later, especially if the infant's diet is poor in substances which contain folic acid or substances which act similarly. We have been making assays of the folic acid content of the various ingredients commonly used in infants' diets but we are not reporting them or the anemias of infancy at this time. The important thing is to realize that there is an association between anemia in the mother and the early development of anemia in the child and to understand the necessity of administering, in many instances, yeast, folic acid, meats and meat products, or various mixtures of these materials. For years it has been recognized that certain infants have megaloblastic anemia and some of these infants have been treated successfully with liver extract. More recently Zuelzer and others described a syndrome of this type which responds to folic acid therapy. We also have observed that folic acid is effective in this type of anemia in infants and children. The point we wish to stress here is that if treatment is administered to the mother and if the baby is fed a diet containing adequate folic acid or substances acting similarly, anemia of this type does not develop.

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MATERIALS AND METHODS

Six patients were selected for study using the following criteria:

1. The patient must have been pregnant within a few weeks prior to the initiation of the study.
2. She must have a macrocytic anemia with red blood cell counts of 2.5 million or less and a color index greater than 1.
3. She must have megaloblastic arrest of the bone marrow.
4. She must have free hydrochloric acid in the gastric juice.
5. She must be untreated or must not have been treated recently enough to interfere with folic acid as a therapeutic agent.

The patients were admitted to the hospital and throughout the course of the study were maintained on a diet which was devoid of meat, meat products, fish, poultry, milk, and eggs.

Daily hematologic examinations included white and erythrocyte counts, hemoglobin determinations, and reticulocyte counts. Certified Trenner pipettes were used for both the white and the erythrocyte counts. A Leitz colorimeter was used for determining in grams the hemoglobin content of the blood. The reticulocytes were counted in wet preparations by the use of a modified brilliant cresyl blue solution of Dameshek. Cell volumes were determined frequently on oxalated venous blood by Wintrobe hematocrit tubes. Bone marrow was obtained by sternal aspiration prior to therapy and at the peak of reticulo-

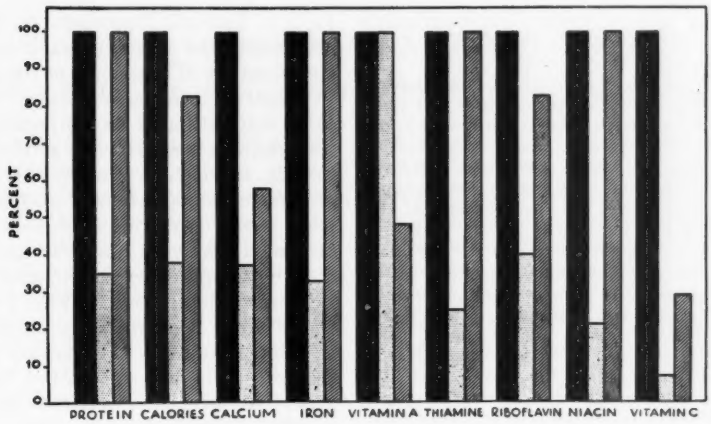

Fig. 1. Nutrients supplied by the diet of a patient with the macrocytic anemia of pregnancy before and after folic acid therapy contrasted to the recommended allowances of nutrients. Black areas, allowance of nutrients recommended by Council on Foods and Nutrition, National Research Council. Dotted areas, nutrients supplied by diet of patient before therapy. Crosshatched area, nutrients supplied by diet of patient after therapy.

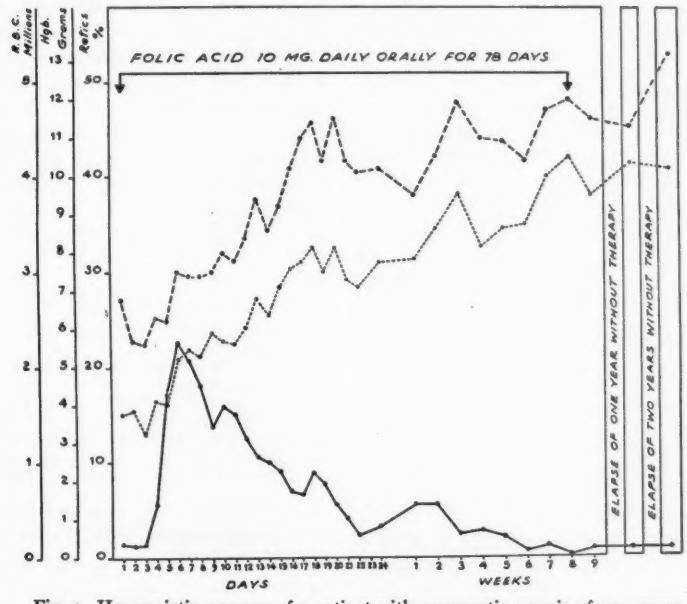

Fig. 2. Hemopoietic response of a patient with macrocytic anemia of pregnancy to folic acid.

cytosis. Differential counts were made on preparations stained while both supravital and Wright's stains.

After the baseline determinations were completed, the patients were given folic acid by mouth. The course in each of the cases is

illustrated in the following representative case history:

C. C., a white woman aged 29 years, was admitted to the hospital 9 days after the birth of her sixth child. At this time she complained of loss of appetite, weakness, and diarrhea.

Her illness began 7 years previously, after the birth of her second child, with gradual loss of appetite, intermittent diarrhea, and loss of strength. At intervals throughout her third, fourth, and fifth pregnancies, she lost her appetite, lost strength, and had diarrhea and burning of the tongue. Two months prior to her admission to the hospital and during the seventh month of her sixth pregnancy, she lost her appetite, developed diarrhea, and her mouth and tongue became so sore she could eat very little food of any kind. The nutrients supplied by her diet during this time are shown in Figure 1. Her diet, which consisted chiefly of foods assayed for folic acid by Angulo and Spies, was also low in folic acid. She became so weak she stayed in bed all the time and for 6 days following the birth of the child she was too weak even to feed herself. She was then brought to the hospital in an ambulance.

As can be seen in Figure 2, her blood values on admission were: red blood cells, 1.50 million; hemoglobin, 6.6 grams (43 per cent); reticulocytes, 2.6 per cent. She was given 10 milligrams of folic acid daily by mouth. The third day after therapy was initiated, she said she felt much stronger than she had for many months, her tongue ceased burning, her desire for food returned, and she ate most of the food offered. On the fifth day of therapy, the reticulocytes rose to 22.7 per cent. Her diarrhea subsided at this time. Her appetite and strength continued to improve and 10 days after therapy was initiated she began walking around the ward and asked to go home. She was kept on folic acid therapy for 78 days during which time she gained 17 pounds in weight. At the end of this time she was instructed as to the foods she should eat and discharged from the hospital. At this time her blood levels were: red blood cells, 4.20 million; hemoglobin, 11.5 grams (75 per cent); reticulocytes, 0.8 per cent.

In the 2 years since she was treated, her diet has been much more adequate than it had been previously (Fig. 1). She has had no recurrence of symptoms and her blood values are: red blood cells, 4.07 million; hemoglobin, 13.2 grams (86 per cent) (Fig. 2).

DISCUSSION

In this clinic we have made many studies on the specificity of the folic acid molecule (2, 4). Various fragments of the molecule are ineffective when given alone or in any combination. The change of the glutamic acid to aspartic acid also makes it ineffective. Folic acid either in its conjugated form or in its free form is effective in producing reticulocytosis, an increase in white blood cells, hemoglobin, red blood cells and platelets in persons who have pernicious anemia, nutritional macrocytic anemia, and the macrocytic anemia of pellegra, pregnancy, and sprue (3, 5). Folic acid should be considered a member of the vitamin B complex, as are thiamine, niacin, and riboflavin. The author believes that the pregnant woman should have 2 milligrams of folic acid daily during the latter months of pregnancy.

SUMMARY AND CONCLUSIONS

1. The megaloblastic anemia of pregnancy, infancy, and early childhood often can be prevented by treating the mother in the late stages of pregnancy with substances having an anti-anemic effect. (If this is not done and if the infant develops megaloblastic anemia, it eventually can be relieved by the administration of folic acid.)

2. It is recommended that this anemia associated with pregnancy be prevented by the administration of 2 milligrams of folic acid daily during the latter months of pregnancy. In a few instances 5 milligrams are required.

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PRIMARY SPLENIC PANHEMATOPENIA

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IN 1944, Doan first used the term splenic panhematopenia to designate a syndrome characterized principally by splenomegaly, panhyperplasia of the bone marrow, and varying degrees of anemia, neutropenia, and thrombocytopenia. His investigations, which ultimately led to the separation of splenic panhematopenia from other splenic syndromes, were first reported in 1939. In the original report, Wiseman and Doan (9) described 4 patients with a chronic neutropenia which was believed to be caused by sequestration and destruction of neutrophilic granulocytes within the splenic sinusoids. The 4 patients underwent splenectomies with restoration of the blood picture to normal and a subsequent report in 1942 (10) stated that the patients had remained in good health. The 4 original patients displayed some anemia and thrombocytopenia as well as neutropenia and in the 1944 report (2) which included additional patients, the term primary splenic panhematopenia was applied to the syndrome. In 1946, Doan and Wright further divided the syndrome into primary splenic panhematopenia on a congenital or familial basis and splenic panhematopenia secondary to some constitutional pathologic process which disturbed splenic physiology. The primary type of splenic panhematopenia may occur as a chronic relapsing disease with intermittent episodes of hemoclastic activity or as a relatively acute disease characterized by prostration and a rapid depression of the cellular elements of the blood. The secondary acquired form of panhematopenia has been observed in Hodgkin's and Gaucher's diseases (3).

Based principally on the results of epinephrine tests, supravitally stained preparations of freshly excised splenic tissue, and the histologic appearance of the bone marrow, Doan and his associates have concluded that the hematologic alterations observed in splenic panhematopenia are due to sequestration of erythrocytes, leucocytes, and thrombocytes within the splenic sinusoids and the destruction of these elements by reticuloendothelial macrophages. In the majority of Doan's patients the subcutaneous administration of 0.5 to 1.0 cubic centimeter of epinephrine produced a significant elevation of the number of circulating erythrocytes, leucocytes, and thrombocytes. Supravitally stained preparations of splenic tissue demonstrated increased phagocytic activity by the clasmatocytes. Bone marrow studies consistently displayed a myeloid hyperplasia and, in many instances, erythroid and megakaryocytic hyperplasia. The authors concluded that congenital hemolytic anemia and idiopathic thrombocytopenic purpura could be included in the same syndrome.

Moore and Bierbaum reported a patient with splenic neutropenia treated successfully by splenectomy. They concluded from supravital staining of fresh splenic tissue that excessive phagocytosis of leucocytes by splenic clasmatocytes was the cause of the neutropenia.

Muether, Moore, Stewart, and Broun did not observe excessive phagocytosis of leucocytes in the spleen in 1 patient. It was not stated, however, whether the microscopic observations were made on supravitally stained tissue or fixed sections.

Rogers and Hall reported a patient with splenic neutropenia which could not be explained on a basis of splenic phagocytic activity. Fixed sections of the spleen were studied. In this patient a chronic hepatitis diagnosed by means of a liver biopsy was present. No other patient thus far reported has had any associated or coincidental hepatic disease.

During the past few years, the diagnosis of primary splenic panhematopenia has been made in 7 instances at the University Hospitals of Cleveland. All of the patients have been subjected to splenectomy. One patient died after operation and a postmortem examination was performed. Some of the observations made upon these patients are at variance with those of Doan and his associates. Our

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TABLE I.—PATIENT E. D. HEMATOLOGIC DATA BEFORE AND AFTER SPLENECTOMY

Date	RBC × 10^6 per c.mm.	Hgb. gm per 100 ml.	WBC per c.mm.	Differential per c.mm		Plat. × 10^3 per c.mm.	Hemt. %	Ret. %	Icterus Index units
				Neut.	Lymp.				
1-29-42	4.20	10.9	7,500	5,700	1,425				
5-26-43	4.52	12.8	8,350						
8-28-44	3.89	11.4	4,600	2,480	1,610	120.59			
12-27-44	2.20	6.6	2,500	1,050	950				
12-29-44	2.25					13.2	18		16
12-30-44			2,250						
1-4-45	2.07	6.3	1,450	203	789	20.0		27	13
1-5-45	Splenectomy. Blood transfusion—500 ml. whole blood								
1-6-45	4.17	11.9	6,050	4,850	454	12.5			

studies offer no support to the hypothesis that the hematologic changes observed in this disease are due to excessive sequestration and phagocytosis of the cellular elements of the blood in the spleen.

The clinical manifestations of primary splenic panhematopenia are variable and depend to a large extent upon the degree of anemia, neutropenia, and thrombocytopenia present. The patients may complain of lassitude, palpitation, and fever. Oral ulceration and indolent ulcers of the lower extremities may be present. Purpura or icterus may or may not be present. Splenomegaly has been present in all but 1 of the patients herein reported.

The peripheral blood shows varying degrees of anemia, neutropenia, or thrombocytopenia or any combination of the three, although neutropenia has been the outstanding feature of our cases. Reticulocytosis and an increase in hematogenous bilirubin as measured by the indirect van den Bergh reaction have been observed in some patients. None of the patients thus far reported here or elsewhere has demonstrated spherocytosis.

Although the exact mechanism producing a reduction of erythrocytes, granulocytes, and thrombocytes in the circulating blood cannot be definitely stated, there is little doubt that this syndrome is separate and distinct from malignant neutropenia, hypoplastic anemia, aleucemic leucemia, Banti's syndrome, and Still's disease.

CASE 1. E. D., 42 years old, white, single female was first admitted to University Hospitals on January 28, 1942, when a diagnosis of diabetes insipidus was made and the symptoms were well controlled by administration of pitressin. Congenital absence of the right radius and partial absence of the left radius were demonstrated by roentgenologic examination. Blood findings at that time (Table I) were not striking. She was readmitted on May 25, 1943, complaining of unsteadiness, vertigo, and paralysis of the left hand. She recovered rapidly from these symptoms and a diagnosis of thrombosis of a small vessel of the right cerebrum was made. Again, blood findings were not remarkable. On this admission, roentgenologic examination of the chest revealed streaky, nodular shadows scattered throughout both lungs and the roentgen diagnosis was fibrosis which might have resulted from atypical pneumonia or sarcoidosis. Her next admission was on August 27, 1944, at which time the spleen was palpably enlarged. At this time the blood showed definite anemia and leucopenia as shown in Table I. Roentgenologic examination revealed the urinary tract and skull to be normal. A diagnosis of splenomegaly and possible sarcoidosis was made. The radiographic appearance of the lungs had not changed in 16 months. Her last admission was on December 26, 1944, when she entered complaining of drenching night sweats for 2 months, worse during the preceding 10 days. She claimed to have sustained a loss of weight of 14 pounds in the preceding 20 days. She had experienced dyspnea and orthopnea. Examination revealed a harsh systolic murmur over the left side of the sternum. The spleen extended 6 centimeters below the costal margin. The liver was palpable 1 to 2 centimeters below the costal margin. On January 2, 1945, a petechial type of purpura appeared over the entire body and the temperature rose to 38.5 degrees C.

The blood findings are shown in Table I. A sternal marrow aspiration was performed and revealed the nucleated cell count to be 139,750 per cubic millimeter, the erythrocyte count 1,840,000 per cubic millimeter, and the hemoglobin 6.5 grams per 100 milliliters. The differential count on the marrow

content was neutrophiles 1.0 per cent, eosinophiles 3.0 per cent, basophiles 0, unsegmented neutrophiles 7.6 per cent, metamyelocytes 7.6 per cent, myelocytes 13.8 per cent, myeloblasts 1.6 per cent, lymphocytes 0.2 per cent, monocytes 0, normoblasts 31.6 per cent, erythroblasts 32.6 per cent, and megaloblasts 1.0 per cent. Fifteen cells in mitosis were seen while counting 500 nucleated cells. These were about evenly divided between red and white cells. The granulocyte:nucleated red cell ratio was 0.53:1.00. There were many megakaryocytes present. The marrow was interpreted as showing increased activity, with all elements participating, and with an especial increase in the nucleated red cells. Other laboratory findings included an icterus index of 16 units, normal bleeding and clotting times, and a normal fragility test (0.44 per cent to 0.36 per cent saline with an identical control). A second icterus index on January 4, 1945, was 13 units. The serum bilirubin was 1.6 milligrams per 100 milliliters. The van den Bergh reaction was weakly positive, direct delayed. There was no increase of urobilinogen or urobilin in the urine as determined by qualitative tests. The reticulocyte count as shown in Table I was 27 per cent.

Splenectomy was performed on January 6, 1945. The spleen was greatly enlarged and was adherent laterally to the parietal peritoneum. It weighed 888 grams and measured 23.5 by 10.0 by 6.5 centimeters. Examination of imprint preparations with the supravital stain (Janus green and neutral red) and Wright stain failed to reveal the presence of any phagocytic clasmatocytes. Examination of fixed tissue sections stained with hematoxylin and eosin revealed fibrous bands adherent to the outer capsule. The connective tissue in the substance of the spleen was not increased in amount. Follicles were numerous and relatively large, many having distinct secondary centers, some of which showed hyalinization and degeneration. The pulp contained lymphocytes, large mononuclear cells and erythrocytes in usual numbers with a distinct increase in the number of eosinophiles. The oxidase stain revealed the presence of a large number of cells containing oxidase positive granules. Throughout, there were many plasma cells, and large mononuclear cells with acicular, relatively large nuclei. Mitoses were observed and there were some nucleated red cells. Sections treated with potassium ferrocyanide and hydrochloric acid showed throughout the pulp masses of blue material indicating the presence of iron. The diagnosis was splenomegaly with myeloid metaplasia and follicular hyperplasia.

Following operation, there was a steady rise in temperature. The blood pressure fell to very low levels and the patient died on the second postoperative day. Only one postoperative blood examination was done as shown in Table I. Autopsy was performed and the following diagnoses made: chronic interstitial pneumonitis, bilateral, marked; chronic encephalitis, marked in hypothalamus; congenital defect in the membranous portion of the interventricular septum, covered by septal leaflet of the tricuspid valve. The disease in the lung was definitely considered not to be the result of tuberculosis or sarcoidosis. It was of an inflammatory nature which might have been the result of an atypical pneumonia, although there was no proof for this. There was marked generalized hyperplasia of the bone marrow throughout. It appeared that the cause of death was right heart failure associated with the pulmonary fibrosis.

CASE 2. H. H., 31 years old, white female was admitted to University Hospitals on July 28, 1942, with a chief complaint of "canker sores" in the mouth, which had occurred intermittently every 3 to 4 months during the preceding 15 years. She also noted increased sensitivity to minor infection, stating that small cuts and injuries healed slowly and remained inflamed for long periods of time. Physical examination revealed a well developed, obese, white woman not acutely ill. There was a deforming scar on the lower lip where one of the ulcers had been removed for biopsy at another hospital. Throughout the buccal mucosa were several small ulcers varying in size from 1 to 5 millimeters in diameter. Her gums bled slightly after she brushed her teeth. Small, nontender submental lymph nodes were present. The spleen was palpable 2 centimeters below the costal margin in the left midclavicular line.

Blood findings on several occasions prior to the subsequent splenectomy are shown in Figure 1. Sternal marrow aspiration was performed with the following results: total nucleated elements, 37,150 per cubic millimeter; erythrocytes 4,780,000 per cubic millimeter; hemoglobin, 12.5 grams per 100 milliliters; neutrophiles, 21.8 per cent; eosinophiles, 4.0 per cent; basophiles 0; immature neutrophiles, 40.8 per cent; myelocytes, 7.0 per cent (all ages and varieties); myeloblasts, 1.2 per cent; lymphocytes, 8.0 per cent; monocytes, 1.8 per cent; normoblasts, 13.2 per cent; erythroblasts, 2.0 per cent; megaloblasts, 0; plasma cells, 0.2 per cent; and megakaryocytes, 0. The granulocyte:nucleated red cells ratio was 5.5:1.00. This was interpreted as representing an active marrow with an increase in the cells of the granulocyte series. An epinephrine test was performed, the results of which are shown in Figure 2. Following the injection of epinephrine the spleen was no longer palpable and the pulse rate increased. Other laboratory data included a blood platelet count of 75,000; reticulocytes, 0.1 per cent; bleeding, coagulation and clot retraction times, normal. Splenectomy was recommended but the patient wished to consider the matter and was discharged on August 3, 1942.

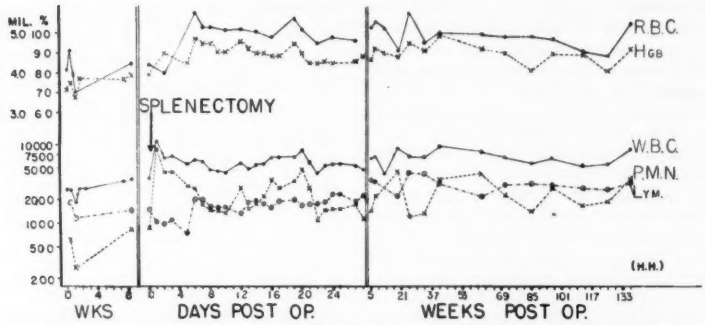

Fig. 1. Patient H. H. Hematologic data before and after splenectomy and follow-up. One hundred per cent hemoglobin equals 15.6 grams per 100 milliliters.

She was readmitted on September 15, 1942. The mild anemia, marked neutropenia, and thrombocytopenia persisted. She had continued to have crops of small ulcers on the oral mucous membranes. On this admission a fragility test showed beginning hemolysis at 0.48 per cent saline with complete hemolysis at 0.32 per cent saline. Control showed values of 0.46 per cent and 0.32 per cent. The icterus index was 5 units. Urobilinogen and urobilin in the urine were not increased as determined by qualitative tests. A diagnosis of primary splenic neutropenia was made and splenectomy was performed on September 17, 1942. Five hundred milliliters of whole blood were administered at the time of operation. The spleen weighed 280 grams and measured 16 by 9 by 4 centimeters. Supravital preparations (Janus green and neutral red) and Wright stained imprints were examined with care and an unusual number of phagocytes could not be demonstrated. Occasional phagocytic cells were present, always containing erythrocytes. Sections stained with hematoxylin and eosin likewise did not demonstrate any unusual phagocytosis. The follicles were large and numerous, and many showed prominent secondary centers. The diagnosis was follicular hyperplasia of the spleen.

Immediately following splenectomy, there was a marked increase in the number of granulocytes, erythrocytes, hemoglobin, and platelets (Fig. 1). It is of interest that the ulcers in the mouth healed within 4 to 5 days after splenectomy. A urinary tract infection, present from the 15th to the 24th day after splenectomy, was treated successfully with sulfathiazole.

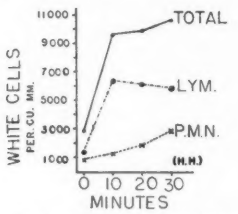

Fig. 2. Patient H. H. Epinephrine test.

During a follow-up period of 140 weeks, there was considerable fluctuation in the number of neutrophiles and lymphocytes in the peripheral blood, although the neutrophiles remained above preoperative levels. It was noted that when mild infections were present, the neutrophiles increased in number. Whether this was true before splenectomy cannot be stated. Occasionally a small ulcer appeared in the mouth, but it never required more than a single treatment with silver nitrate. She gained a considerable amount of weight and felt well. The red blood cell count and hemoglobin levels were a little higher after operation than before and the platelets were present in considerably increased numbers. A small number of target cells were present on the blood films. From Figure 1, it can be seen that there tended to be an inverse relationship between granulocytes and lymphocytes during the entire period of observation following splenectomy.

CASE 3. Patient M. B., 36 years old, unmarried, white female, was admitted to University Hospitals on August 13, 1942. Her complaint was "tiredness in the legs, especially on climbing stairs, and a feeling of fullness in the abdomen, especially after eating a full meal." These symptoms had been present for about a year. She stated that at about the time of onset of symptoms, while running in the dark, she struck a wire which was strung about waist high. She was catapulted over the wire and experienced severe pain in the left upper quadrant during the following day, and milder pain for a week. She

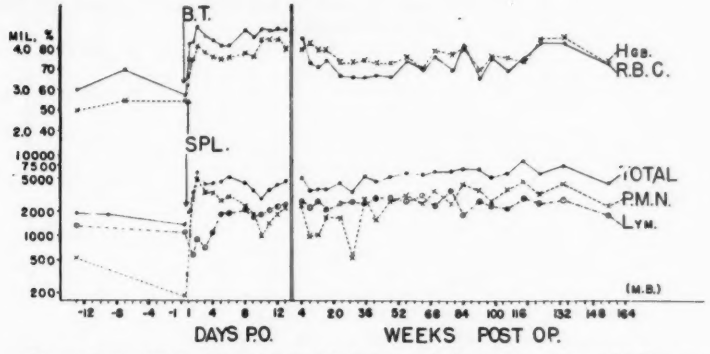

Fig. 3. Patient M. B. Hematologic data before and after splenectomy and follow-up; 100 per cent hemoglobin equals 15.6 grams per 100 milliliters.

gained about 5 pounds in weight "immediately" and remarked that her dresses felt tight. She added, further, that the gain in weight was limited to the abdomen. She did not consult a physician. Physical examination revealed a well developed and nourished patient who did not appear acutely ill. There was no enlargement of the lymph nodes. A harsh systolic murmur was heard over the cardiac apex. The spleen was greatly enlarged, extending to the umbilicus inferiorly and to the mid-line medially. The remainder of the physical examination was within normal limits. Laboratory examination revealed urine to be normal. Blood findings prior to operation are shown in Figure 3. The icterus index was 7.0 units, and the erythrocyte fragility test showed beginning hemolysis at 0.46 per cent saline and complete hemolysis at 0.34 per cent saline with a control having values of 0.42 per cent and 0.30 per cent. A repeat test showed beginning hemolysis at 0.46 per cent with complete hemolysis at 0.36 per cent with a control having values of 0.40 per cent and 0.32 per cent. Bleeding, coagulation, and clot retraction times were within normal limits.

On August 20, 1942, the urine contained a slightly increased amount of urobilinogen and urobilin. Roentgenologic examinations of the abdomen and gastrointestinal tract were normal except for the presence of the enlarged spleen. The basal metabolic rate was plus 19. On August 14, 1942, a sternal marrow biopsy was performed. Examination of imprint smears stained with Wright's stain and fixed sections stained with hematoxylin and eosin revealed generalized hyperplasia with marked red cell activity. There was a marked reduction in fat and the ratio of nucleated red cells to granulocytes was increased. The differential cell count on the marrow imprints showed percentages of: neutrophiles 6.2, eosinophiles 0.4, basophiles 0.4, unsegmented neutrophiles 13.2, myelocytes 9.2, myeloblasts 1.6, lymphocytes 3.0, monocytes 0, normoblasts 54.0, erythroblasts 10.6, and megaloblasts 1.4. The granulocyte nucleated red cell ratio was 0.47:1.00.

A diagnosis of primary splenic neutropenia was made and splenectomy was performed on August 24, 1942. At operation the spleen appeared to be "five times" its normal size. The patient received 900 milliliters of citrated blood on the day of operation. The spleen weighed 1800 grams and measured 29 by 19 by 5 centimeters. A supravital preparation (Janus green and neutral red) was made and an extensive search made for phagocytic cells. Few such cells could be found and those present contained erythrocytes. Phagocytes containing granulocytic cells could not be demonstrated. Imprint smears stained with Wright's stain and fixed sections stained with hematoxylin and eosin likewise failed to reveal any unusual phagocytosis. The final diagnosis was hyperplasia of the spleen without other histologic abnormality.

Rapid recovery followed the splenectomy. Symptomatic improvement was marked and has continued to the present time. The hematologic findings are shown in Figure 3. It will be noted that immediately following operation, the granulocytes rose to a high level, then over a period of time fell to a lower level, although never as low as preoperative levels. Over a period of 3 years, the granulocytes remained at a considerably higher level than before the operation. The initial increase in red cell count and hemoglobin was contributed to, at least in part, by the blood transfusions given at the time of operation. It will be noted that a mild anemia persisted for most of the 3 year observation period, although there was some increase in red cell count and hemoglobin, especially during the last year. The patient received ferrous sulfate and liver extract for several months at a time without any

TABLE II.—PATIENT N. J. P. HEMATOLOGIC DATA BEFORE AND AFTER SPLENECTOMY AND FOLLOW-UP

Date	RBC × 10^6 per c.mm.	Hgb. gm. per 100 ml.	WBC per c.mm.	Differential per c.mm.				Plat. × 10^3 per c.mm.	Hemt. %	Ret. %	Icterus index units
				Neut.	Lymp.	Mono.	Eos.				
9-15-44	1.20	5.5	2,000	560	1,180	200	80	50		1–2	
9-21-44	3.06	11.5	3,000	840	2,040	60	60	100	35.7		6
9-28-44	2.91	10.8	3,400	476	2,820	68	34	80			
10- 2-44	2.70	9.8	4,300	602	3,480	172	43			1	
10- 9-44	2.88	8.0	4,000	Discharged from hospital							
11-21-44	1.27	5.5	4,750	1,425	2,850	475	0	103		0.8	7
11-24-44	2.00	8.3	2,900	522	2,030	319	0	100		1.8	
12- 1-44	3.90	14.0	4,500	2,250	1,575	540	135		55.0		
12- 7-44	Discharged from hospital										
5- 2-45	1.47	4.7	4,000	1,920	1,800	200	80				
5- 4-45	1.87	7.0	4,100	982	2,950	41	41				
5- 7-45	4.50	10.9	6,500	1,170	5,000	260	65	135			
5- 8-45								110		0.4	
5-23-45	3.98	11.4	3,000								
5-25-45	Splenectomy										
5-26-45	4.23	11.5	7,250	4,560	2,660	0	0				
5-28-45	4.00	11.5	6,500	5,840	520	130	0				
5-30-45	4.68	14.4	6,300	3,470	2,645	126	63				
6- 8-45	5.79	13.3	5,250	2,640	2,420	0	63				
6- 9-45	Discharged from hospital										
6-25-45	4.38	13.0	4,650	2,020	1,955	395	186	N*			
7-16-45	3.51	10.9	6,300	2,047	3,210	32	536	Red.*			
8-14-45	4.70	10.0	8,600	3,880	4,550	172	0	N*	33.3	0.8	
11-26-45	3.11	10.7	6,500	2,145	4,160	130	65	130		2.1	
3-14-46	3.96	12.3	7,450	4,395	2,384	149	521				
4- 6-46	5.40	15.3	11,200	2,688	4,816	1,792	112	260			
9- 3-46	4.60	11.5	15,000	10,500	3,750	300	450				

N is normal number of platelets, Red. is reduced number.

effect on the anemia. Fragility tests done on a few occasions since splenectomy showed a gradual increase in resistance of the erythrocytes to hypotonic saline. Seventy-eight weeks after operation, hemolysis began at 0.36 per cent saline and was complete at 0.18 per cent saline. Some target cells could be observed in the blood at this time. The blood platelets, which were reduced in number to as low as 49,000 before operation, rose to 602,000 a month later and have continued to be present in increased numbers since. Of interest in the hematologic course shown in Figure 3 is the fact that there was a gradual increase in total white cell count and granulocyte count over a period of 3 years. Also of interest is the observation, again, of the inverse relationship of granulocytes and lymphocytes. From Figure 3 it will be noted that generally when granulocytes are increased, lymphocytes are decreased, and vice versa.

CASE 4. N. J. P., 2 year old, white female, was admitted to the pediatric service for the first time on September 15, 1944. At this time a history of tonic convulsions of 6 weeks' duration was elicited from the parents. Her past history revealed a normal full term birth. Nutrition had been consistently poor. At the age of 1½ years, she was treated for an anemia of undetermined type at another hospital.

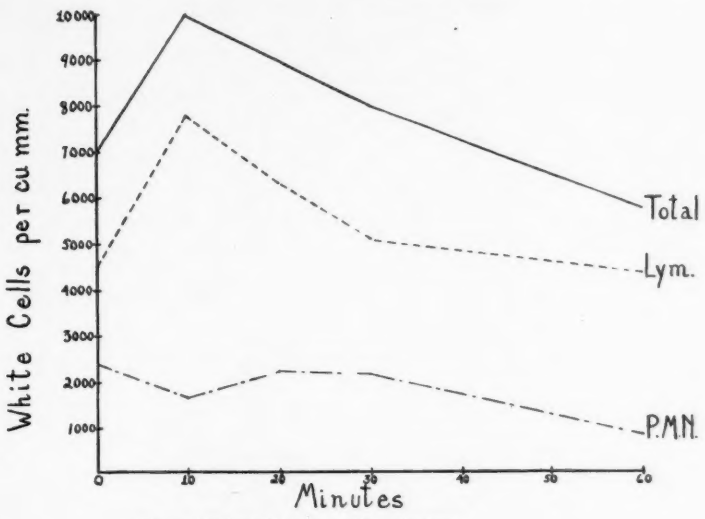

Fig. 4. Patient N. J. P. Adrenalin test.

Physical examination revealed a pale, chronically ill child. Her weight was 7.5 kilograms. Her skin was pale and the subcutaneous tissue scant. The heart was questionably enlarged to the left and a systolic murmur at the apex was transmitted to the axillae. The spleen was palpable just beneath the costal margin, and the liver was palpable 3 centimeters below the costal margin.

Initial blood findings showed a hemoglobin of 5.5 grams per 100 milliliters, erythrocytes 1,200,000 per cubic millimeter, and leucocytes 2,000 per cubic millimeter. A differential count showed segmented neutrophiles 28.0 per cent, lymphocytes 58.0 per cent, large mononuclears 10.0 per cent, and eosinophiles 4.0 per cent. A platelet count showed 50,000 thrombocytes per cubic millimeter, and reticulocyte counts were less than 2.0 per cent. Several blood transfusions were given during the hospital course. Sternal marrow aspiration showed a nucleated cell count of 38,300 per cubic millimeter, erythrocyte count 3,240,000 per cubic millimeter, and hemoglobin 10.4 grams per 100 milliliters. A differential marrow count showed neutrophiles 18.6 per cent, eosinophiles 4.6 per cent, basophiles 0.6 per cent, unsegmented neutrophiles 14.6 per cent, metamyelocytes 15.2 per cent, myelocytes 10.8 per cent, myeloblasts 4.4 per cent, lymphocytes 16.4 per cent, monocytes 0.8 per cent, normoblasts 10.6 per cent, erythroblasts 2.0 per cent, megaloblasts 0.8 per cent, plasma cells 0.6 per cent and megakaryocytes 0. The granulocyte:nucleated red cell ratio was 5.13:-1.00. The marrow was considered essentially normal. Radiographic examination of the chest showed slight enlargement of the cardiac silhouette toward the left. An electrocardiogram was normal. At the time of discharge September 9, 1944, the hemoglobin was 8.0 grams per 100 milliliters, erythrocytes 2,880,000 per cubic millimeter, and leucocytes 4,000 per cubic millimeter. A tentative diagnosis of primary splenic neutropenia was made.

The patient was readmitted on November 21, 1944, and again on May 2, 1945. The blood findings before and after operation are found in Table II. An epinephrine test is shown in Figure 4. On May 25, 1945, a splenectomy was performed. The spleen weighed 32 grams and measured 7.0 by 4.5 by 2.0 centimeters. Two accessory spleens were also removed. Microscopic examination of fixed sections showed no demonstrable phagocytosis, moderate follicular hyperplasia, and hemosiderin pigmentation. A final diagnosis of splenic panhematopenia was made.

The patient was readmitted on several occasions for follow-up studies and acute respiratory infections, as shown in Table II. On her last admission on September 3, 1946, the hemoglobin was 10.5 grams per 100 milliliters, erythrocytes 4,600,000 per cubic millimeter, and leucocytes 15,000 per cubic millimeter. A differential count showed segmented neutrophiles 70 per cent, lymphocytes 25 per cent, monocytes 2 per cent, and eosinophiles 3 per cent. This patient subsequently died at another hospital on July 3, 1947. The cause of death is unknown.

CASE 5. L. B., 50 years old, white, married female, was admitted to University Hospitals on July 12, 1945, with a complaint of pain in the joints of several

TABLE III.—PATIENT L. B. HEMATOLOGIC DATA BEFORE AND AFTER SPLENECTOMY AND FOLLOW-UP

Date	RBC × 10^6 per c.mm.	Hgb. gm. per 100 ml.	WBC per c.mm.	Differential per c.mm.				Plat. × 10^3 per c.mm.	Hemt. %	Ret. %
				Neut.	Lymp.	Mono.	Eos.			
7-13-45	4.53	12.5	1,380	97	952	317	13			
7-14-45			1,575							
7-16-45	4.33	11.5	850	68	630	153	0	134.8	42	0.2
7-17-45	4.70	12.5	740	89	443	177	30			
7-19-45		11.5	650	58	409	169	13			
7-19-45	Splenectomy. 1000 ml. citrated whole blood transfusion									
7-19-45	3.96	11.5	2,950	1,770	912	236	29			
7-20-45		12.4	7,400	5,820	664	888	0	296.0	38	
7-21-45	3.49	10.4	9,750	7,410	878	1,360	48			
7-23-45		11.3	8,900	7,520	580	712	89		36.5	
7-28-45	3.83	10.6	7,850	5,320	1,020	1,255	157			
8- 1-45		10.4	5,150	3,040	1,030	929	154			
8- 2-45	Discharged from hospital									
10- 1-45	3 73	11.2	9,600	1,055	7,680	672	192			
11- 5-45	4.03	12.2	5,550	389	1,609	888	166			
1- 7-46		13.6	5,200	676	3,796	624	104			
4-13-46	4.48	14.2	6,000	1,340	2,940	1,440	120			
7- 5-46		15.0	9,600	3,744	4,800	768	288			
12- 7-46	4.61	16.1	11,250	2,812	7,200	562	1,012			
12-23-46		13.4	6,500							
3-18-47	4.80	14.3	6,050							
9-30-47	4.42	14.2	5,350	1,391	3,263	535	160			

years' duration, which had become more acute during the past 3 months. The symptoms were thought to be the result of hypertrophic arthritis and she was admitted for study. Physical examination revealed a well nourished woman who did not appear acutely ill. There was slight sclerosis of the retinal arteries. The liver was palpable about 1 centimeter below the costal margin and the spleen was enlarged to 3 centimeters below the costal margin and was firm and nontender.

Blood findings are shown in Table III and Figure 5. It can be observed that there was a marked progressive drop in the total white blood cell count, especially of the neutrophiles but also of the lymphocytes. Sternal marrow biopsy was done and imprint smears showed an active marrow. The differential count on Wright stained imprint smears was neutrophiles 2.2 per cent, eosinophiles 4.2 per cent, basophiles 0.2 per cent, unsegmented neutrophiles 12.4 per cent, metamyelocytes 11.0 per cent, myelocytes 21.6 per cent, myeloblasts 1.4 per cent, lymphocytes 10.6 per cent, monocytes 0.2 per cent, normoblasts 26.8 per cent, erythroblasts 7.0 per cent, megaloblasts 0, and plasma cells 2.4 per cent. The granulocyte:nucleated red cell ratio was 1.57: 1.00. Fixed tissue sections of sternal marrow showed increased cellularity, with both erythrocytic and granulocytic cells participating. There appeared to be an increased number of eosinophiles present. The blood platelet count was 134,800, the bleeding time 2 minutes, and the clotting time 4 minutes with normal clot retraction. The prothrombin content (Quick's method) was 78 per cent of normal, the icterus index 3 units, the reticulocyte count 0.2 per cent, and the hematocrit 42 per cent. A diagnosis of primary splenic panhematopenia was made in which it was noted that the granulocytic series of white cells was particularly involved. Splenectomy was recommended. Preceding operation the temperature slowly rose until the day before operation it reached 40.2 degrees C.

Splenectomy was performed on July 19, 1945. At operation the spleen was found to be adherent to the diaphragm and was removed with some difficulty. During the operation considerable hemorrhage took place. The patient received 1000 milliliters of citrated whole blood during and immediately following the operation. The spleen weighed 575 grams and measured 20 by 12 by 5 centimeters. Supravital preparations (Janus green and neutral

red) and Wright stained imprints made immediately after removal of the spleen failed to reveal any phagocytic clasmatocytes. Fixed tissue sections showed the red pulp to be moderately engorged with blood and there was an increase in the number of cells present. Some of these were plasma cells and in the region adjacent to the capsule, particularly, there were large polygonal cells with clear vacuolated cytoplasm. Malpighian follicles were larger than usual and had prominent secondary centers. Sections stained with Sudan IV showed a moderate number of mononuclear cells which contained Sudanotropic material. Sections stained with potassium ferrocyanide and hydrochloric acid showed a considerable amount of iron throughout the pulp. There was no demonstrable phagocytosis. The diagnosis was follicular hyperplasia.

For 11 days after operation, the patient had fever. She received penicillin, and dicumarol was administered for a time because the possibility of a splenic vein thrombosis was considered. Table III shows the blood findings during a follow-up period of 2 years. The neutrophiles, while not at normal levels, have remained well above preoperative levels. A mild anemia has persisted. The blood platelet count was 296,000 on the first postoperative day and has remained at normal levels since.

CASE 6. D. T., a 66 year old, white female was admitted on the medical service of University Hospitals on December 6, 1945. She gave a history of having had recurrent, slowly healing ulcers on the legs for 5 years. Her local physician had treated these with penicillin and tyrothricin without obtaining any significant healing. Physical examination revealed a well developed but poorly nourished white woman appearing chronically ill. The patient had a marked deforming atrophic arthritis, involving most of the joints. There was a large ulcer on the right lower leg measuring 2.5 by 3.5 centimeters. The surface of the ulcer showed little granulation and was covered with a foul smelling, purulent discharge. The spleen was palpable 6 centimeters below the left costal margin in the midclavicular line.

Blood findings are shown in Table IV. Sternal marrow aspiration was performed with the following results: myeloid-erythroid content, 3.5 per cent; fat content, 0.5 per cent; nucleated cell count, 58,750 per cubic millimeter. The differential cell count was neutrophiles 7.4 per cent, eosinophiles 5.0 per cent, basophiles 0, unsegmented neutrophiles 22.4 per cent, metamyelocytes 11.4 per cent, myelocytes 12.6 per cent, myeloblasts 3.2 per cent, lymphocytes 4.8 per cent, monocytes 0.4 per cent, normoblasts 29.2 per cent, erythroblasts 2.6 per cent, megaloblasts 0.4 per cent, and plasma cells 0.6 per cent. Megakaryocytes were abundant. The granulocyte: nucleated red cell ratio was 1.80:1.00. This was interpreted as representing an active marrow with a moderately marked left shift of the granulocyte series and with an abundance of red cell forming elements. The clinical diagnosis was primary splenic panhematopenia, and a splenectomy was performed

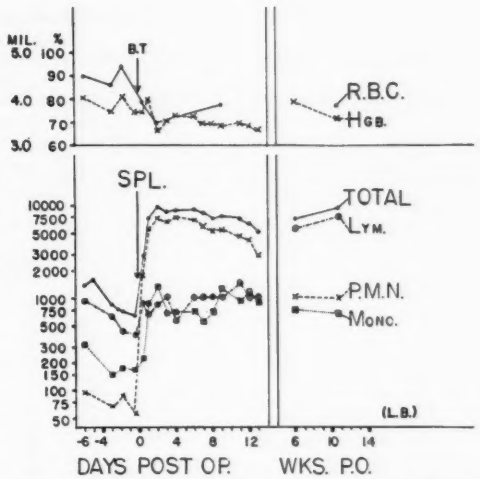

Fig. 5. Patient L. B. Hematologic data before and after splenectomy and follow-up; 100 per cent hemoglobin equals 15.6 grams per 100 milliliters.

on December 21, 1945. Five hundred milliliters of whole blood was administered at the time of operation. The spleen weighed 650 grams and measured 21.8 by 10.6 by 3.9 centimeters. Representative sections were stained with hematoxylin and eosin, Foote's silver stain, and Masson's trichrome strain. The blood sinuses were slightly dilated and filled with well preserved erythrocytes. Scattered throughout the pulp were large numbers of cells showing phagocytic activity. Some of these had one nucleus, others had two or, at the most, three. The particles which had been phagocytized could not be identified, but most of them did not appear to be blood pigment. The diagnosis was chronic splenomegaly, consistent with the clinical diagnosis of primary splenic panhematopenia. There were no postoperative complications. The blood picture became more normal and the leg ulcer began to heal. Table IV shows the postoperative hematologic data over a follow-up period of nearly 2 years.

The patient was readmitted to University Hospitals on November 4, 1947, with an ulcer of the left great toe, due to trauma. Blood findings at that time are shown in Table IV. The ulcer was treated with Dakin's solution with good results, and the patient was discharged on the 12th hospital day. Although the blood findings were still not within normal limits, the chronic ulcers on the lower extremities remained healed, and a new ulcer, the result of definite trauma, yielded rapidly to treatment.

CASE 7. A. F., 36 years old, married, white female, was admitted to University Hospitals on March 3, 1947. She had been told following a routine physical examination 4 months prior to admission that she had a "low white count." She had been troubled

TABLE IV.—PATIENT D. T. HEMATOLOGIC DATA BEFORE AND AFTER SPLENECTOMY AND FOLLOW-UP

Date	RBC × 10^6 per c.mm.	Hgb. gm. per 100 ml.	WBC per c.mm.	Differential per c.mm.				Plat. × 10^3 per c.mm.	Hemt. %	Ret. %
				Neut.	Lymp.	Mono.	Eos.			
12- 6-45	3.25	9.8	950	66	389	161	266	Inc.*	29	
12-10-45	3.90	9.7	2,450	122	1,543	392	294	N.*		3.6
12-12-45	2.96	9.5	2,000	240	680	720	280			
12-15-45	3.31	9.4	1,100	176	616	132	176	300		
12-21-45	Splenectomy. Blood transfusion 500 ml.									
12-21-45	4.08	12.6	2,950	2,124	59	206	0	Inc.*		
12-22-45			9,150	6,908	549	1,281	91	N.*		
12-23-45	4.54	12.3	8,350	6,930	501	417	208	Inc.*		
12-24-45			11,700	9,301	760	1,111	292	Inc.*		
12-26-45	4.23	12.8	6,650	4,256	697	931	697	Inc.*		
12-27-45			6,450	4,740	354	741	516	Inc.*		
12-28-45			6,300	4,660	567	535	409	Inc.*		
12-31-45	4.49	13.1	7,100	4,500	887	1,136	532	Inc.*		
1- 3-46			5,950	3,140	892	1,011	684	Inc.*		
1- 5-46			4,200	2,163	861	399	693	Inc.*		
1- 9-46	Discharged from hospital									
11- 4-47	4.00	13.3	5,200					Inc.*		
11- 5-47	3.68	1 .7	6,100	2,623	1,952	671	671	800		
11-10-47	3.77	12.1	3,950	2,271	1,027	256	296	Inc.*		

N. is normal number of platelets, Inc. is increased number.

with numerous furuncles, sore throats, and on one occasion a perineal abscess, during the preceding few months. At the age of 7, the patient had rheumatic fever, and was told that her heart had been affected. Three years before admission, the patient experienced an attack of rheumatoid arthritis and since then had had some migratory pain in practically all joints.

Physical examination revealed a well developed female apparently in good health. Small furuncles were observed on the face, arms and hands. The oral pharynx was slightly hyperemic. Shotty, nontender cervical, axillary, and inguinal lymph nodes were palpable. The spleen was palpable 3 centimeters below the costal margin. The remainder of the physical examination was within normal limits. The urinalysis was negative. Blood studies showed hemoglobin 13.4 grams per 100 milliliters, erythrocytes 4,750,000 per cubic millimeter, leucocytes 1,900 per cubic millimeter, and platelets 269,600 per cubic millimeter. The differential cell count was unsegmented neutrophiles 6 per cent, segmented neutrophiles 3 per cent, lymphocytes 52 per cent, monocytes 26 per cent, eosinophiles 12 per cent and basophiles 1 per cent. The serum proteins were 6.6 grams per 100 milliliters, the albumin 3.9 grams per 100 milliliters, the globulin 2.7 grams per 100 milliliters, and the albumin-globulin ration 1:4. The icterus index was 9 units. A thymol turbidity test was 2.6 units. A bromsulfalein test showed 5 per cent retention in 15 and 45 minutes.

Sternal marrow aspiration revealed a myeloid-erythroid content of 6.0 per cent, fat content 0.5 per cent, erythrocyte content 36.0 per cent, and plasma content 57.5 per cent. The nucleated cell count was 64,750 per cubic millimeter. The differential cell count on the marrow was neutrophiles 5.0 per cent, eosinophiles 7.2 per cent, basophiles 0, unsegmented neutrophiles 9.2 per cent, metamyelocytes 12.0 per cent, myelocytes 18.8 per cent, myeloblasts 1.0 per cent, lymphocytes 1.4 per cent, monocytes 0.6 per cent, normoblasts 40.6 per cent, erythroblasts 4.0 per cent, megaloblasts 0, and plasma cells 0.2 per cent. The granulocyte:nucleated red cell ratio was 1.2: 1.00. The megakaryocytes were slightly increased in number, and immature forms were present. An epinephrine test was performed with the results shown in Figure 6.

A diagnosis of primary splenic panhematopenia was made and a splenectomy was completed without difficulty on March 8, 1947. The patient received 500 milliliters of citrated blood on the day of operation. The spleen weighed 405 grams and measured 16 by 11 by 5.5 centimeters. Supravital (Janus green and neutral red) studies of spleen tissue showed an occasional phagocyte ingesting adult erythro-

cytes or neutrophiles. These were not numerous and only a few could be found on prolonged search. There was an increased number of eosinophiles present. Wright stained imprint of splenic tissue revealed an occasional very large phagocytic cell containing one or more neutrophiles, erythrocytes, or nucleated red cell. These were not numerous and only 3 or 4 were found on prolonged search. Fixed tissue sections were not striking. No phagocytic cells could be seen. The germinal centers of the follicles appeared to have been "washed out" and contained fewer cells than normally seen. The final diagnosis was moderate hyperplasia of the spleen. The patient's postoperative convalescence was uncomplicated, and she was discharged on her 12th postoperative day. Hematologic findings, before and after operation, are recorded in Table V.

These patients presented the findings described by Doan (2) as occurring in primary splenic panhematopenia. Neutropenia, anemia, and thrombocytopenia occurred in all patients and varied from mild to severe. Splenomegaly was constantly present, but variable in degree. Purpura was observed, depending upon the degree of thrombocytopenia. Oral ulcerations were present in 1 patient and chronic ulcers on the legs of another patient, both of whom had severe, and presumably chronic, neutropenia. Mild jaundice occurred in only 1 of the 7 patients. The bone marrow was hyperplastic in all instances.

Examination of the spleen, in all instances, and an autopsy performed on 1 patient, did not reveal the presence of any other disease that might have accounted for the hematologic disturbance. There was no suggestion that leucemia or other diseases of the lymphblastoma group were present. Findings characteristic of Banti's disease, Gaucher's disease, or Still's disease were not present. The histologic picture was not characteristic or specific, and generally no more than mild follicular hyperplasia could be demonstrated.

These patients also demonstrated certain characteristics which were somewhat unexpected. In spite of moderate or severe anemia, reticulocytosis was absent, except in 1 patient, E. D. Occurrence of reticulocytosis after splenectomy would tend to have been obscured, if present, by blood transfusions given at the time of operation.

The absence of visible jaundice, little or no elevation of the icterus index, and no increase of urinary urobilinogen were also notable.

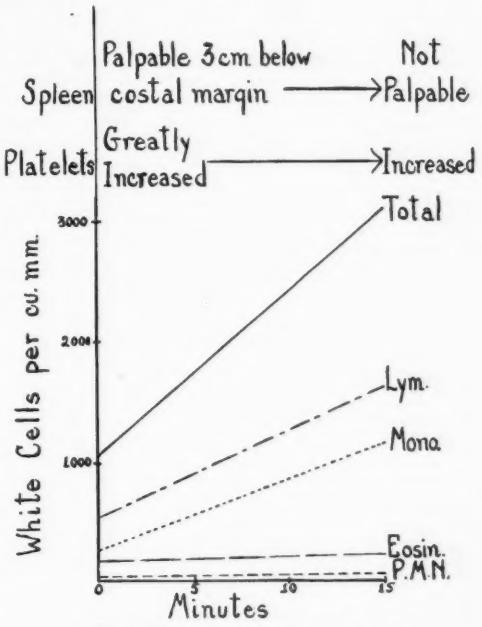

Fig. 6. Patient A. F. Adrenalin test.

With the exception of 1 patient, E. D., who also demonstrated reticulocytosis, the usual evidence of hemolysis was absent even in patients with severe anemia. Since fecal urobilinogen studies were not made on these patients, it cannot be said that conclusive proof against increased production of bile pigments has been offered. It is conceivable that even with excessive production of bile pigment due to rapid breakdown of erythrocytes, the liver was able always to clear the blood stream and prevent jaundice. In such a case, it must be presumed that the increased amount of urobilinogen was excreted entirely in the feces and not at all in the urine. That such a condition existed in all these patients seems unlikely, even though possible.

Because of these findings, it seems obvious that the anemia in these patients was not clearly hemolytic in origin and is not comparable to congenital hemolytic anemia. The most outstanding difference between the anemia of congenital hemolytic anemia and that of primary splenic panhematopenia, however, is the constant presence of spherocytosis in

TABLE V.—PATIENT A. F. HEMATOLOGIC DATA BEFORE AND AFTER SPLENECTOMY AND FOLLOW-UP

Date	RBC × 10^6 per c.mm.	Hgb. gm. per 100 ml.	WBC per per c.mm.	Differential per c.mm.				Plat. × 10^3 per c.mm.	Hemt. %	Ret. %	Icterus index units
				Neut.	Lymp.	Mono.	Eos.				
3- 3-47	4.75	13.4	1,900	57	988	494	228	269.6	41	1.2	9
3- 8-47	Splenectomy. 500 ml. citrated blood transfusion										
3- 9-47			9,650	6,948	337	1,968	48				
3-10-47	4.37	12.4	10,900	4,850	1,199	2,343	436	399.9			
3-11-47			8,800	4,532	748	704	836				
3-12-47			7,100	4,544	994	639	639				
3-13-47			7,100	4,402	1,278	497	639				
3-14-47			6,000	3,300	1,560	420	480				
3-15-47			7,900	3,318	2,765	632	711				
3-18-47			4,200	2,268	1,092	546	210				
3-19-47			7,650	3,748	2,065	1,147	459				
3-20-47	Discharged from hospital										
4- 1-47	4.38	13.4	6,400	2,848	2,112	1,056	256	Inc.*			
5- 1-47	4.72	14.0	5,700	2,679	1,795	1,083	57	Inc.*			
8- 8-47			5,600	2,184	2,800	504	112	Adeq.*			

Inc. is increased numbers of platelets, Adeq. is adequate number.

the former and its constant absence in the latter disease. The usual patient with congenital hemolytic anemia exhibits leucocytosis and thrombocytosis at the time of crisis, unlike the patients in this series. Reticulocytosis, jaundice, and an increase in urinary urobilinogen are likewise common, if not constant, findings in congenital hemolytic anemia.

Idiopathic thrombocytopenic purpura also differs in certain characteristics from primary splenic panhematopenia. Splenomegaly is notably absent. There is no alteration in the erythrocytes unless hemorrhage has occurred. A leucopenia, but not specifically neutropenia, exists in some cases, although leucocytosis may be present if hemorrhage has occurred. Even so, it might be conceivable that idiopathic thrombocytopenic purpura could represent an instance of primary splenic panhematopenia in which the destructive action of the spleen was selective for platelets alone and in which enlargement of the spleen does not occur. In idiopathic thrombocytopenic purpura, however, specific changes are seen in the megakaryocytes which were not seen in any of these patients and have not been reported by others.

Failure to demonstrate excessive phagocytosis in the spleens of these patients after careful study of supravital, Wright stained, and fixed tissue preparations makes it doubtful that phagocytosis is the mechanism responsible for the production of primary splenic panhematopenia. Other authors (6) have likewise commented on their inability to demonstrate phagocytosis. Moore and Bierbaum were able to demonstrate it in 1 of 3 cases.

A tendency for a delayed leucocyte response in certain of these patients, especially M. B. and H. H., with a slow return toward normal over a period of many months was also noted. If excessive phagocytosis, occurring solely in the spleen, was responsible for the occurrence of the hematologic disorder, it would be reasonable to expect that splenectomy would produce an immediate, persistent, and complete return of the hematologic picture to normal. Indeed, if the spleen is the sole organ concerned in the production of the disease, whatever the mechanism, such an immediate, complete response might be expected. The abrupt return to normal in patients with congenital hemolytic anemia and in some cases of idiopathic thrombocytopenic purpura fol-

lowing splenectomy is well known, although it is not uncommon to observe a gradual, rather than abrupt, increase in platelets following splenectomy in cases of thrombocytopenic purpura.

In our experience, the epinephrine test has not been of aid in the diagnosis or interpretation of the mechanism of this syndrome. The rise in leucocyte count following the administration of epinephrine is the result of the appearance of increased numbers of lymphocytes in the peripheral blood, with little change in the number of polymorphonuclear neutrophiles. The change in erythrocyte, hemoglobin, and platelet levels (not recorded in the charts) has been too small to be subject to interpretation, and similar changes have been observed in normal individuals and even in individuals who have undergone splenectomy. These findings, coupled with failure to find increased numbers of myeloid cells in the spleen, either free or phagocytized, make it more doubtful that sequestration and phagocytosis of cells in the spleen can be considered the primary mechanism of the syndrome.

The role of the spleen in this disease is, therefore, not clearly defined at this time, especially if patients with this syndrome continue to show absence of excessive phagocytosis. An alternative explanation, which seems to us to be better correlated with the findings, is that the spleen has a regulatory effect on bone marrow as proposed by Dameshek in idiopathic thrombocytopenic purpura. The anemia, not clearly hemolytic, may be the result of failure of proper discharge of erythrocytes from the marrow. The presence of neutropenia and thrombocytopenia could be explained, likewise, on the basis of suppression of discharge of these elements from the marrow. Direct proof, however, of such a mechanism is lacking at this time. Ungar (8) has demonstrated an endocrine-like relationship between the pituitary and the spleen in protein metabolism and claims to have isolated from the spleen a pure crystalline material which is responsible for this effect. Singer, Miller, and Dameshek likewise have claimed to demonstrate that lysolecithin, produced by the spleen, has a regulatory effect on erythrocytes. Further study is necessary to determine whether the hematologic findings in primary splenic panhematopenia might be the result of a similar regulatory mechanism.

SUMMARY

1. Seven patients are described with the clinical and laboratory findings characteristic of primary splenic panhematopenia. After splenectomy 1 patient died; the 6 others were markedly improved.

2. Jaundice, urobilinogenuria and reticulocytosis were not as evident as would have been expected if the anemia was of a simple hemolytic nature.

3. Following splenectomy, hematologic improvement tended to be gradual and prolonged rather than immediate and complete.

4. Excessive phagocytosis of myeloid elements could not be demonstrated in the spleens of these 7 patients.

5. Examination of the spleens in all instances, and one autopsy, did not reveal the presence of any known disease. The spleens were enlarged and generally showed varying degrees of follicular hyperplasia. In only 1 patient was there an increase of myeloid elements in the splenic pulp.

6. It is questionable that congenital hemolytic anemia and idiopathic thrombocytopenic purpura are members of this syndrome.

7. Since excessive phagocytosis could not be demonstrated in these patients, it is suggested that some regulatory action of the spleen on bone marrow may be the mechanism responsible for the hematologic disorder.

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JULY, 1949

THE INDICATIONS FOR HYSTERECTOMY

THE word hysterectomy is derived from the Greek,—*Hustera*, uterus and *Extome*, excision. Therefore, it means excision of the uterus. This term is applied to the uterus alone and does not include the tubes and ovaries. If the oviducts and ovaries are also removed, the term hysterectomy must be followed by unilateral—right or left, bilateral salpingo-oophorectomy, or hysterosalpingo-oophorectomy. Hysterectomy may be total or subtotal, and may be performed for either malignant or benign disease of the uterus and adnexa. Synonyms for total hysterectomy are: complete hysterectomy and panhysterectomy, while those for subtotal hysterectomy are: partial, supravaginal, supracervical and fundic hysterectomy. The extirpation of the uterus may be performed through the abdomen—abdominal hysterectomy, or through the vagina—vaginal hysterectomy.

Carcinoma of the uterus, cervix or corpus, sarcoma of the uterus and chorionepithelioma are the malignant diseases for which hysterectomy is generally indicated. In the presence of malignant disease the total operation is always performed and should be accompanied by the ablation of the adnexa, because of the frequent metastases to these structures. While the majority of carcinomas of the cervix uteri are treated by radium and high voltage x-ray, the radical abdominal panhysterectomy, commonly referred to as the Wertheim operation, is reserved, by some surgeons, for malignant disease of the cervix uteri in certain group I and group II cases, League of Nations classification. This intervention consists of the suppression of the entire uterus, the tubes, the ovaries, the pelvic connective tissue after dissection of the ureters, the vagina almost entirely, and the obturator and iliac glands. The radical vaginal hysterectomy, proposed by Schauta for the same indication, namely malignant disease of the cervix, does not afford as satisfactory exposure as does the abdominal intervention and has, therefore, never acquired the popularity of the latter among the majority of pelvic surgeons.

In the treatment of malignant disease of the corpus uteri, such as carcinoma, adenoacanthoma and chorionepithelioma, radium or high voltage x-ray should be applied, and, in the course of five to six weeks this should be followed by a panhysterectomy and bilateral salpingo-oophorectomy. Exposure to radium or x-ray so modifies or eliminates the carcinomatous cells that their implantation elsewhere at the time of operation is greatly reduced or totally prevented. In sarcoma of the uterus radium or x-ray are not employed because

these agents have very little effect on this type of tumor, but the total hysterectomy with the excision of the adnexa should be performed as soon as the diagnosis is established. Malignant neoplastic disease of the oviducts and ovaries demands the total removal of the uterus with the pathological adnexa.

The indications for hysterectomy for benign disease are fibromyoma, the most common indication, uterine prolapse when it is accompanied by uterine bleeding or when the uterus is pathological,—vaginal hysterectomy; inversion of the uterus, when gangrene and infection have set in; myometrial hypertrophy associated with hyperplasia of the endometrium and hemorrhage; cesarean hysterectomy, in the presence of fibromyomas, infection, and hemorrhage; pelvic inflammatory disease, specific, tuberculous and puerperal, when the involvement of these structures is marked, and in endometriosis, interna and externa, when the pathology is extensive and cannot be treated by conservative measures. When hysterectomy is performed for benign uterine disease, the adnexa are removed if pathological, and conserved, as a rule, if normal.

In myometrial hypertrophy with endometrial hyperplasia and hemorrhage, and in certain intramural fibromyomas, which in size are not larger than a three month gestation, hysterectomy enters into competition with irradiation by means of radium or high voltage x-ray. Irradiation will control the bleeding, and the small fibromyomas will regress after this form of therapy, but the organs remaining *in situ* may be the seat of carcinoma of the uterus or ovaries a number of years later—fifteen years from my observation. Irradiation in the treatment of these conditions is a valuable procedure in the poor surgical risk, in one whose physical condition precludes the performance of an operation so extensive as a hysterectomy, but, when there is no contraindication, hysterectomy, with or without the ablation of the adnexa, as the case may be, shows a certain superiority over irradiation since it insures the patient against future disorders of these organs.

The question of total versus subtotal hysterectomy is still unsettled. The literature of the past two decades definitely shows that an increasing number of surgeons are performing the complete operation as routine, and reserving the subtotal operation for special conditions, this being a complete reversal of the opinions of a half a century ago. The advantages of the total over the subtotal hysterectomy are: absolute prophylaxis against carcinoma of the cervical stump, protection against benign tumors of the cervix, such as cervical fibromyomas, the avoidance of the so called bleeding cervix from benign causes, and the prevention of an annoying leucorrhea which frequently originates in the cervix after the suppression of the uterine corpus. The disadvantages are said to be: the operation is more difficult of execution, the operative mortality and morbidity are higher, the danger of injury to the bladder and ureters is greater, and finally. the vagina is shortened. However, it has been proved by statistics, that in the hands of surgeons well trained in the performance of this operation, the mortality and morbidity of panhysterectomy need not be greater than that of subtotal hysterectomy, and that also, in the hands of surgeons so trained, injuries to the bladder and ureters are uncommon. The shortening of the vagina need be but very slight if the vagina is cut close to the cervix, and after its closure, it is well supported by the fascia endopelvina, aided by the round and uterosacral ligaments. An increasingly large number of operators are of the opinion that the advantages overbalance the disadvantages of the complete operation.

LOUIS E. PHANEUF.

VAGINAL HYSTERECTOMY

THE removal of the uterus by the vaginal route is an operation of considerable age, in spite of what one might judge from the discussions at gynecological assemblies. Probably no operation has had as many "ups and downs" as has vaginal hysterectomy. Preceding the introduction of aseptic technique, the mortality following the abdominal removal of pelvic tumors was so high that it was performed only under the greatest urgency. At a meeting of the American Gynecological Society in 1880 a series of 119 abdominal hysterectomies for fibroids was reported with a mortality of 64 per cent. At the 1886 meeting, it was stated that abdominal hysterectomy was so highly dangerous that it was rarely warranted.

In 1876 Czerny revived the vaginal hysterectomy technique of Souter of Constance, and it rapidly came into vogue both in Europe and in this country, and abdominal hysterectomy was performed but rarely. Large series of vaginal hysterectomies were reported from all medical centers. Great dexterity in technique was developed so that even large fibroids were removed by morcellation, and both ovarian and uterine tumors, even complicated by inflammation of the appendages, were removed vaginally with far greater safety than by the abdominal route. In 1884 Mundé stated that the day following a vaginal hysterectomy for cancer lasting two hours, the patient usually appeared no worse than if she had been delivered of child.

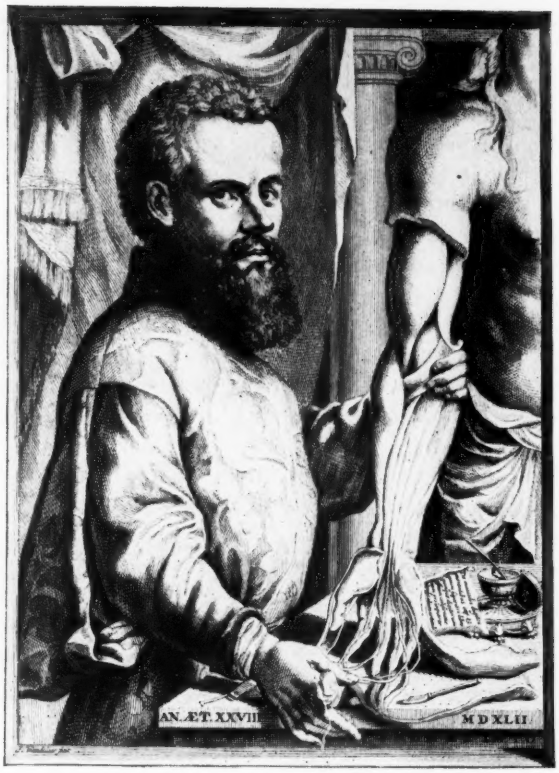
When at the end of the last century aseptic surgery became perfected, the abdomen was entered with relative safety. Gynecologists largely deserted the vaginal attack on pelvic disease and entered the abdomen, so that in addition to doing the indicated surgery, they might also remove the chronic appendix. They learned about cecum mobile, Jackson's membrane, Lane's kink, and devised procedures for their attention, and they shortened the mesentery of the colon, if it appeared longer than pleased them. Meddling minds found much to do. Follicular cysts were punctured or cauterized, and if no cysts were present, the ovaries were resected if the patient menstruated too much or too little. In most clinics vaginal hysterectomy was abandoned entirely and a generation of gynecologists grew up totally unacquainted with the vaginal approach to pelvic disease. As well known a gynecologist as Floyd Keene of Philadelphia, the head of a large and important teaching unit, lived and died without ever performing a single vaginal hysterectomy nor did he ever see his former chief, John Clark, do one. In only a few centers in this country was the operation performed, though it still survived in the German clinics.

American gynecologists, spending their residencies in Germany, were impressed with the easy recoveries of the patients operated upon vaginally as compared to the convalescences of patients operated upon abdominally, and upon their return reintroduced vaginal surgery to American gynecology. The mortality after vaginal hysterectomy, under comparable conditions, is much lower than after abdominal hysterectomy. A shorter period of anesthesia is required. Shock is extremely rare. Vomiting and gas pains are much less severe. Bowel obstruction is very unusual. Paralytic ileus hardly ever occurs. Bleeding from the vaginal hysterectomy itself is usually less than from an abdominal incision alone. The patient is not so sick and the hospital stay much shorter. The period of convalescence is not so protracted and the patient may resume her usual duties in a much shorter time. Postoperative hernia and eventration are, of course, unknown.

Now that we know that chronic appendicitis is largely mythical and the procedures accessory to an abdominal hysterectomy are frequently harmful and meddlesome, it is high time that vaginal hysterectomy assumes its rightful place in gynecology. It is interesting to note how those who persist in perfecting themselves in the technique of vaginal hysterectomy gradually disregard more and more of the contraindications so insistently laid down by those with little or no familiarity with the operation. When the operator's technique is finally perfected, he finds it easier to remove the uterus through a nulliparous or virginal pelvis, if the vaginal vault is ordinarily capacious and is not constricted or infantile, than if relaxation is considerable.

Under certain conditions, a vaginal hysterectomy is strictly indicated and no other procedure is even a passable substitute. A young woman, for example, under thirty-five has an uncontrollable menorrhagia. She has had several curettements with only temporary or no relief. All styptics have failed and all the directions of the endocrine wizards have been conscientiously but unsuccessfully followed. The patient is extremely obese or is otherwise a poor operative risk, and an abdominal hysterectomy would be extremely hazardous. Under these conditions radium is ordinarily administered. The patient's menorrhagia will be relieved, but the annoyances of the menopause will be added to her already long list of complaints. Estrogens cannot be safely given and the patient may later have the delayed effects of the radium. Under these circumstances a vaginal hysterectomy might very safely be performed; I have never yet substituted radium therapy in a patient in whom vaginal hysterectomy is indicated. However, if one is to confine the use of vaginal hysterectomy to only such patients as present absolute indications, he will not have the necessary dexterity to operate upon such patients when the necessity arises. The Kjelland forceps is frequently a fetal life saver. If the obstetrician does not familiarize himself with its use as mid and low forceps, where it is not necessary, he will not know one blade from the other when great familiarity is necessary for the occasional case in which it is strictly indicated.

Is a gynecologist competent when he gives radium to a patient who really needs a vaginal hysterectomy because he is not able to do the particular operation that is indicated? Is a man a specialist, in a field as restricted as is gynecology, unless he can do the special operations applicable to that province? Particularly, would one expect that, when a surgeon is certified by an examining board which limits the area of his activities, he would be able to perform every operation peculiar to his restricted sphere? N. SPROAT HEANEY.



ANDREAS VESALIUS

Bruxellenſis

Invictiſſimi Caroli V. Imperatoris Medicus.

Vesalius demonstrating the muscles of the upper extremity; title page, *Opera Omnia* of Boerhaave and Albinus, 1725.

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ANATOMICAL TABULAE AND INITIAL LETTERS IN VESALIUS' FABRICA AND IN IMITATIVE WORKS

BARRY J. ANSON, Ph.D. (Med. Sci.), Chicago, Illinois

I. VESALIUS' CENTURY

THE sixteenth century was marked by exuberant achievements in all fields of human endeavor. This was the century of William Shakespeare (Fig. 1), Francois Rabelais (Fig. 2), Sir Thomas More (Fig. 3), Francis Bacon (Fig. 4), Galileo Galilei (Fig. 5), and of Girolamo Fracastoro, Leonardo da Vinci (Fig. 6) and Ambroise Paré (Fig. 7); of John Calvin (Fig. 8) and Martin Luther (Fig. 9); of Miguel de Cervantés (Fig. 10), Sir Francis Drake (Fig. 11) and Sir Walter Raleigh; of Henry VIII of England (Fig. 12) and Henry II of France. It was the age of Giovanni Marinello, Carlo Ruini, Niccolo Machiavelli, Hans Holbein, Guilelmus Rondeletius, Richard Hakluyt, Nicolas Monardes, Tiziano Vecellio, Ulysses Aldrovandi, Benvenuto Cellini, and Albrecht Dürer.

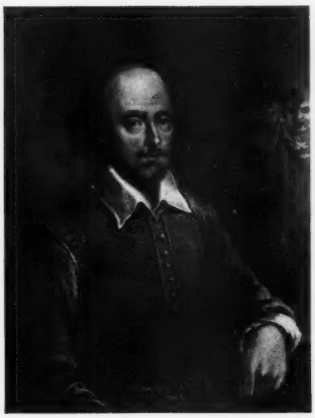
To Shakespeare we owe the robustious humor of Falstaff and the ethereal plaint of Ophelia; the macabre intrigue of Macbeth and the whimsy and prank of Puck and Bottom; the reverie of Juliet and the stratagem of Caesar; the gemmy beauty of Cleopatra and the sinister hideousness of three witches. Comparably, Francois Rabelais excelled as a story teller, as did Sir Thomas More and Francis Bacon in the fields of statecraft and philosophy. Galileo Galilei found a magnetic core for the Earth, and Leonardo da Vinci and Tiziano Vecellio painted masterpieces, to fasten wings of glorious hope on mankind's concepts of heavenly aspiration. Ambroise Paré, surgeon to four successive kings of France, not only spread new knowledge of surgery, but also wrote expansively of his journeys with the armies of the French kings. Girolamo Fracastoro, in his treatise of contagion, set forth a prevision of infection by micro-organisms. Martin Luther and John Calvin liberated religion from hierarchic domination. While the churchmen brought clerical balm to the soul, Giovanni Marinello, with mundane practicality, laid the groundwork for epidermal rehabilitation in his volume on cosmetics, perfume, and hair-dyes. Aware of the importance of cavalry in the game of war, Carlo Ruini prepared an illustrated treatise on the anatomy of the horse. Niccolo Machiavelli codified military and diplomatic methods and practices for the guidance of aggressive monarchs. Keeping pace with the expansion of ambitious nations, Johann Huttichius compiled his collection of voyages and discoveries in the New World, and Richard Hakluyt published his account of the principal navigations of the English nation. In the field of zoology Guilelmus Rondeletius wrote on the subject of fishes, and in that of botany Nicolas Monardes described therapeutically the "rare and singular vertues" of the herbs, trees, oils and stones brought from America. The biological sphere was further widened by the contents of folios, from the hand of Ulysses Aldovandi, on various aspects of natural history, including the occurrence of human monsters. Benvenuto Cellini worked exquisitely with precious stones and metals, while Albrecht Dürer excelled in the handling of wood engravings.

The First Brödel Memorial Lecture, read at the Chicago (September, 1948) meeting of the Association of Medical Illustrators.

More than a half century ago (1894), Max Brödel came to Baltimore, from Leipzig, at the behest of Dr. Franklin P. Mall, for an immediate association with Dr. Howard A. Kelly, and later, with Drs. Thomas S. Cullen and William S. Halsted, and their eminent colleagues.

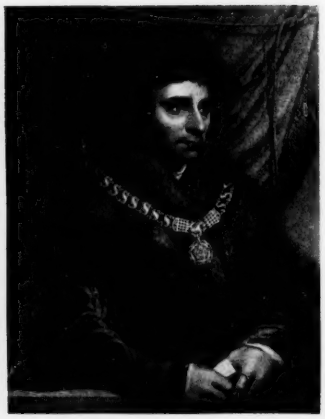
Mr. Brödel was an enemy of plagiarism—against which larcenous practice Vesalius had inveighed, and the malignant abuses of which he had suffered deeply. Aware of the fact that sometimes larceny is a way of taking what one cannot create, and recognizing that medical pictures were being done by artists untrained and, therefore, inescapably dependent upon predecessors, Mr. Brödel established the first department of art as applied to medicine.

For biographical material, dealing with the life and achievements of Mr. Brödel, the reader is referred to the following articles: J. Am. M. Ass., vol. 110, no. 11, March 12, 1938, pp. 817–818, p. 823; ibid., vol. 117, vol. 9, August 30, 1941, pp. 668–672; Bull. Med. Libr. Ass., vol. 33, no. 1, Jan. 1945, pp. 6–29.



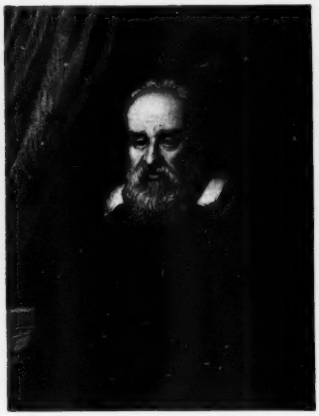
William Shakespeare (1564–1616).

Francois Rabelais (1490–1553).

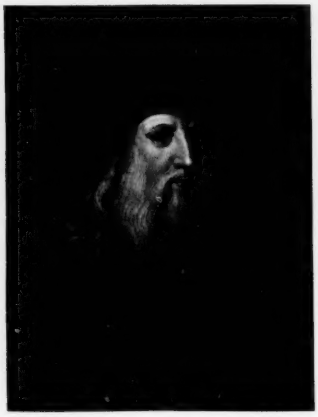


Sir Thomas More (1480–1535).

Francis Bacon (1561–1626).



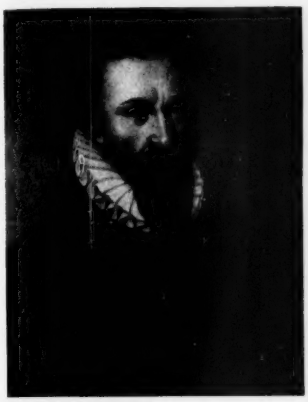
Galileo Galilei (1564–1642).



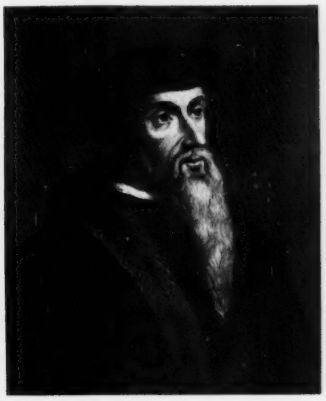
Leonardo da Vinci (1452–1519).

Figs. 1 to 6. Illustrious personnages of Vesalius' century.

As a consequence, the sixteenth century was an age of illustrious accomplishment. In the fields of history and cartography, writers and mapmakers kept pace with the widening geographical sphere; prescient monarchs patronized these and similar projects, furnishing the monetary fuel to kindle the creative imaginations of their talented subjects. Scholarly clergymen broke away from thralldom, and converted religion into an exercise governable by the worshipper. In the physical sciences the laws of cosmic behavior were propounded. For the communal and closer needs of mankind, political doctrines were formulated; some of these were harshly realistic, others consolingly utopian—but all of them expansive. The marvels of the plant world caught afresh the eyes of man. Not only were the herbs of the Old World described and figured, but also those of the new continents—with ardent commentary on their curative value. Comparably, the animals were studied. The ancient works on natural history were printed in encyclopedic form; new, but equally fabulous creatures were described from the globe's enlarging menagerie; and the horse, among domesticated mammals, being useful to the husbandman and the soldier, was anatomized and made comprehensible as a living instrument in a world already anxious to annihilate space. Artists and craftsmen in wood and metal, liberally patronized and commissioned, attained new heights

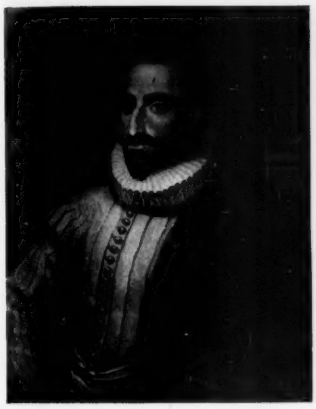


Ambroise Paré (1510–1590).



John Calvin (1509–1564).

Martin Luther (1483–1546).



Miguel de Cervantés (1547–1616).

Sir Francis Drake (1540–1596).

Henry VIII (1491–1547).

Figs. 7 to 12. Personnages; sixteenth century, continued.

of productive skill. The artists in particular found outlet for their fervor in preparation of magnificent illustrations for those of their contemporaries who labored in the biological sciences. Briefly, there were playwrights, play-actors and essayists; inquisitive ecclesiastics and searching scientists; conquerors and chroniclers; monarchs and monastics; artists and artisans; political planners and pietistic pieceworkers.

It would have been strange, indeed, had this surge of creative force failed to inspire some inquisitive and sagacious scholar to unriddle the mystery of human fabric. Men were now thinking with anthropocentric bias, and the ultimate product of Nature's perfect contriving could not be long neglected. Appropriately, the study of man was lifted to a station of suitable loftiness in the folio treatise of Andreas Vesalius.

2. PRIMITIVE ANATOMIC FIGURES[1]

Only when the early books, antecedent to, or contemporaneous with, the appearance of the

[1]Almost all of the anatomic illustrations reproduced herein were photographed from the original works in the Archibald Church Library of Northwestern University Medical School. However, for material from manuscripts and incunabula, the writer was dependent chiefly upon the following sources: *History and Bibliography of Anatomic Illustration*, Ludwig Choulant (transl. and ed., Mortimer Frank). Chicago: University of Chicago Press, 1920; *Atlas of the History of Medicine, Anatomy*, J. G. De Lint. New York: Paul B. Hoeber, 1926.

The pictures of personnages (Figs. 1 to 12) were copied from the following source-books: *Portraits of Illustrious Personnages of Great Britain*, London Printing and Publishing Co.; *Imperial Dictionary of Universal Biography*, Glasgow: William Mackenzie.

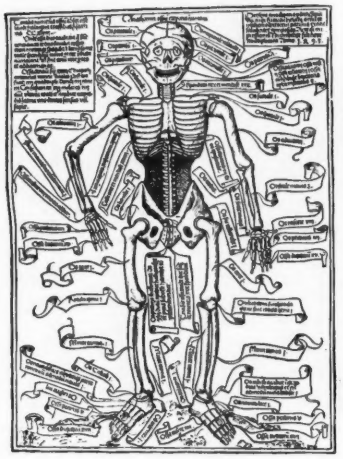


Fig. 13

Fig. 14

Fig. 15

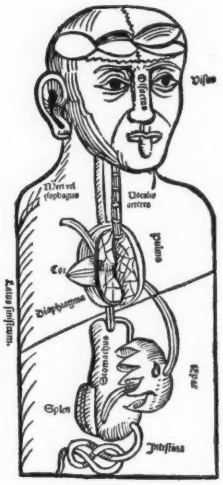


Fig. 16

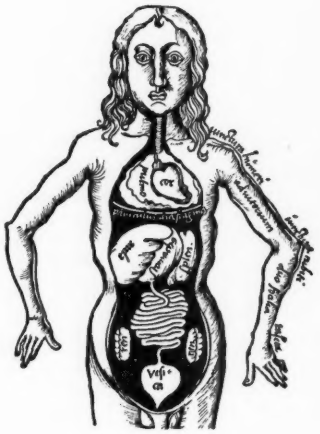


Fig. 17

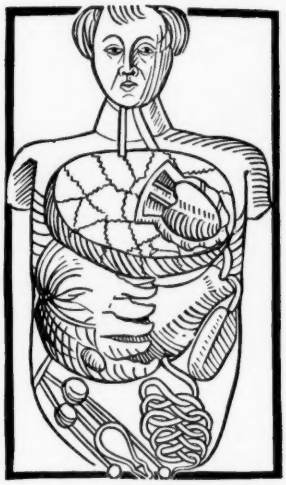


Fig. 18

Figs. 13 to 18. Primitive anatomic illustrations.

Fig. 13. The Nuremberg skeleton (Richard Helain, published in 1493).

Fig. 14. Skull, from Charles Estienne (*De Dissectione Partium Corporis Humani, Libri Tres*, 1545).

Fig. 15. Thoracic dissection from the *Anatomia* of Guido de Vigevano (1478).

Fig. 16. Thoracic and abdominal viscera, and cerebral ventricles, from Johann Peyligk's *Philosophia Naturalis Compendium* (1499).

Fig. 17. Viscera, from Gregor Reisch's *Margarita Philosophia* (Johann Schott, 1503).

Fig. 18. Visceral figure, from Magnus Hundt's *Antropologium de Hominis Dignitate Natura et Proprietatibus* (1501).

Fabrica, are examined, does the excellence of the Vesalian figures become impressive. For skeletal morphology, Vesalius' forebears would have referred to the Nuremberg plate, which displayed the bones articulated and named in bannered labels (Fig. 13), or to some equally primitive representation of man's supportive framework. Details would later have been supplied by the

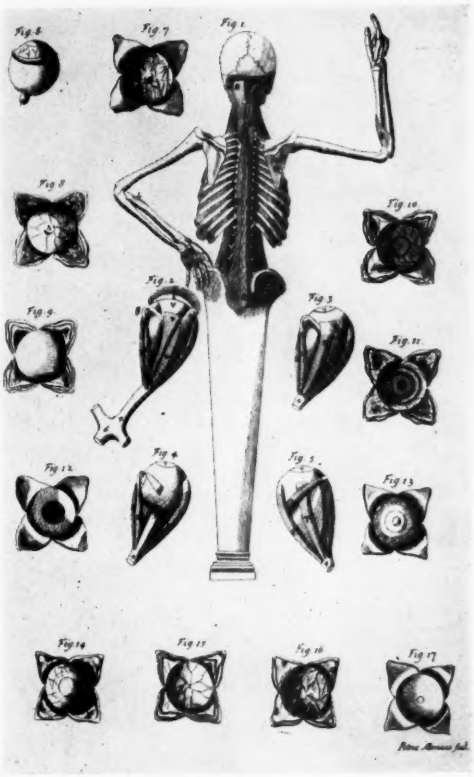


Fig. 19

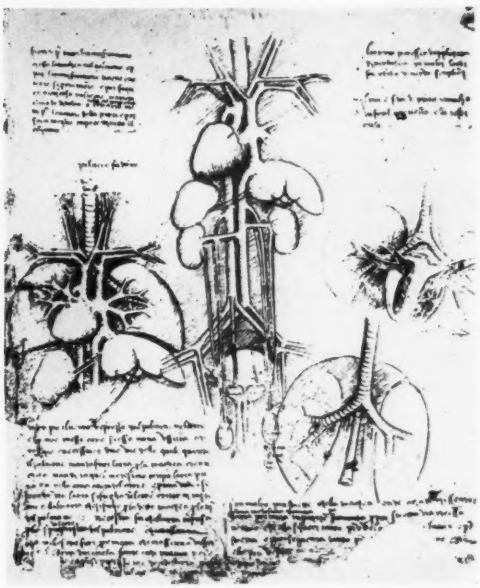


Fig. 20

Figs. 19 and 20. Illustrations from works by Vesalius' contemporaries.

Fig. 19. Plate from the *Tabulae Anatomicae* of Bartolommeo Eustachio (Venice, 1749).

Fig. 20. Sketches by Leonardo da Vinci.

figures of Charles Estienne (Fig. 14), whose lengthy folio, *De Dissectione Partium Corporis Humani, Libri Tres*, was published in 1545. For the dissector, recourse could have been made to the work of Guido de Vigevano, which recorded successive anatomic levels in serial lamination, pictured a method of anatomizing the cadaver (Fig. 15), and made such fabulous additions to human anatomy as the seven-celled uterus. Other writers stressed the configuration and topography of the thoracic and abdominal organs, and the disposition of the ventricular spaces within the brain. For example, in the visceral figure from Peyligk's *Philosophia Naturalis* (1499), the morphology of the brain and of the thoracic and abdominal organs, is handled in stylized fashion (Fig. 16). The cerebral ventricles are superimposed upon a calvarium. Pulmonary and coronary anatomy is diagrammatized; the lungs and heart lie cranial to an oblique line which represents the diaphragm. The gourd-shaped stomach is clasped on one side by a flattened spleen, on the other by a crenate liver; an abbreviated intestine is tied in a lover's knot. Equally rude is the visceral figure from Hundt's *Antropologium*, published in 1501 (Fig. 18), and the comparable illustration from Reisch's *Margarita Philosophia*, which appeared in 1503 (Fig. 17). In Reisch's illustration (Fig. 17), as in Peyligk's (Fig. 16), the various labels are placed upon or near the structures. In the picture from Reisch's work (Fig. 17), the liver (labelled *epar*), the stomach, and the spleen are of more natural form; yet, curiously (perhaps through the delineator's error), the small intestine, shown uncoiled but neatly piled, opens into the urinary bladder (*vesica*). The reader views the body from the front, not as in Reisch's picture, wherein the head is revolved to face the specimen's back (Fig. 16). In the illustration from Hundt's *Antropologium*, the heart is merely superimposed upon the lungs (Fig. 18); a relatively enormous liver, with crenate border, clasps a gourd-shaped stomach; the latter is connected with the spleen by a "duct" which is quite as

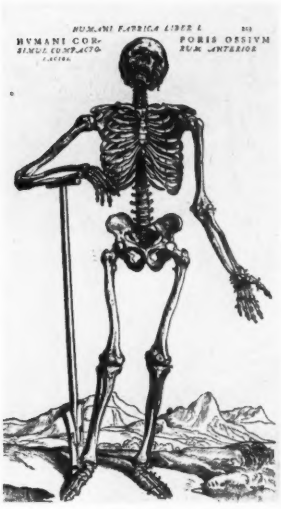


Fig. 21

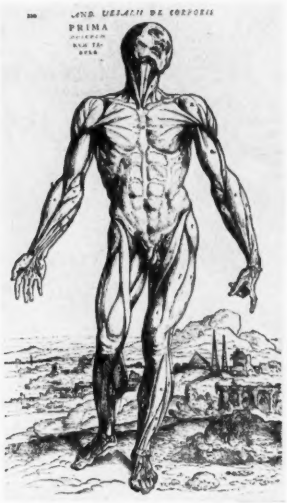


Fig. 22

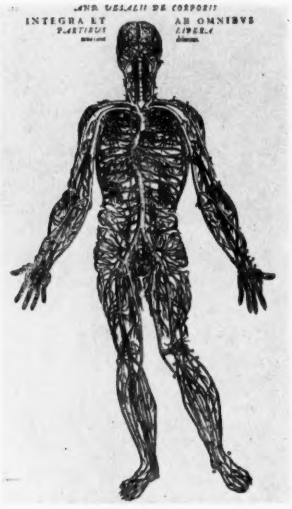


Fig. 23

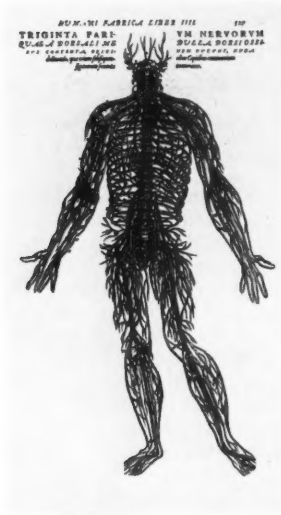


Fig. 24

Fig. 25

Fig. 26

Figs. 21 to 26. Plates from the 1555 edition of Vesalius' *De Corporis Humani Fabrica Libri Septem.*

Fig. 21. The skeleton, in ventral view.
Fig. 22. The musculature, viewed from the front.
Fig. 23. Superior and inferior caval veins and tributaries.
Fig. 24. The nerves in dorsal view.
Fig. 25. Contents of the thoracic cavity.
Fig. 26. The brain and the calvarium.

capacious as the esophagus (cf. Fig. 16, label *meri vel esophagus*). Not content with a short jejunoileum tied in a single knot, or with one piled like a hose, the artist puts the small intestine into a serial interlacement. The kidneys and ureters are conveniently displaced; the urinary bladder,

with some justification, is pictured as being a syringe. Duct-like channels connect the kidneys with the testes.

It is not surprising to find that in many of the illustrations prepared prior to, and during, the time of Andreas Vesalius, at least as much effort was made to portray the form of the liver, the ventricular spaces of the brain, and the rooms in the heart, as was expended in the effort to delineate bones, muscles, and guts. In these sequestered retreats resided the soul of man, locally and progressively rectified to attain, ultimately, celestial perfection in the cerebrum.

These were the pictorial heritage of the sixteenth century; they were derived from the text of Galen of the second century, repeated by Rhazes in the tenth. To the scholars of ancient Greece, and imperial Rome, to the clergy of the crusading Church, and to the valiant and acquisitive conquerors and colonizers of the New World, the body of man remained an unexplored microcosm. However, before the sixteenth century had reached its fifth decade, ambitious study had been pursued with such renascent vigor that several great volumes on human anatomy had been either completed or planned.

Fig. 27. Initial letter, from a manuscript copy of the works of Galen.

3. CONTEMPORARIES OF VESALIUS

Actually, four renowned anatomists of the period were engaged in original anatomical investigations: Giovanni Canani, whose fasciculus of

ANDREAE VESALII
DE CORPORIS HVMANI FABRICA LIBER
SECVNDVS, LIGAMENTIS OSSA CARTILA-
gines q; musculi committentibus, & Musculis, voluntario-
rum motuum instrumentis, dedu. atus: & figuras apti
proprias, uti nunc dextribitur,
proponens.

T 3 PRIMA

HVMANI FABRICA LIBER II. 163

DE MVSCVLIS PALPEBRARVM.
Caput. 12.

Fig. 28, left. Large initial letter T from the 1555 edition of Vesalius' *Fabrica*. Introducing the second book (on bones and ligaments).

Fig. 29. Smaller initial letter P from the same edition. Introducing chapter IX of the second book.

Fig. 30

Fig. 31

Fig. 32

Fig. 33

twenty-seven muscle figures, published in 1542, was later destroyed by the author himself, on the conviction that his work would be inferior to that of Vesalius; Bartolomeo Eustachio, whose plates, long mislaid, were not published until 1714 in the *Tabulae Anatomicae* (Fig. 19); Leonardo da Vinci, whose sketches, in facsimile, alone stand in evidence of his genius (Fig. 20); and Andreas Vesalius, author of the *De Humani Corporis Fabrica, Libri Septem*, the most influential volume ever composed on the gross structure of the human body. Vesalius' works, in revised form, were still copied two hundred years after the publication of his monumental folio.

4. VESALIUS: LIFE AND WORK

In the true sense, Vesalius' rise, and his brilliant showering of knowledge upon lesser men, were meteoric in intrinsic character and in lasting effect. His own life was so brief as to be a transient luminosity; but when regarded as the source of lesser luminaries, whose claim to fame de-

Fig. 34

Fig. 35

Figs. 30 to 35. Large initial letters; *Fabrica*, 1555 edition. Introducing the dedication and the several books.

pended upon his genius, then, indeed, does he appear as the center of a constellation (portrait, frontispiece).

Vesalius was born in Brussels on the last day of the year 1514. At an early age he matriculated in the nearby University of Louvain. For his graduate thesis he composed a paraphrase of the popular medieval compendium of medicine, the ninth book of Rhazes, to correlate the Arabic writings with those of Galen. In this endeavor he took special pleasure, since a commentary on the books of Rhazes had been prepared by his grandfather. Vesalius' father was one-time apothecary both to the Emperor Maximilian, and to his son, the Archduke Charles, and to the latter when he became Emperor Charles V of Austria.

With an inquisitiveness nurtured by careful study, Vesalius, at the age of eighteen, travelled to Paris to obtain a medical education. At the outbreak of the third Franco-German war, in 1536, Vesalius returned to the University of Louvain. Shortly after the publication of the *Paraphrasis*, Vesalius journeyed to Italy, selecting for residence the prosperous and enlightened Venice. There he practiced minor surgery and conducted public demonstrations. While there, he met Jan Stephan van Calcar, whom he subsequently selected to illustrate his magnificent works. During his stay in Venice, Vesalius prepared his own edition of Guenther's *Institutiones anatomicae* in 1538; others followed, to 1613. Of all the many commentaries on Galen's works printed during the late Renaissance, few proved more popular than Johann Guenther's manual of four books, which had been specifically prepared for medical students. Vesalius also edited the *Opera Omnia* of Galen; with the aid of other scholars, he converted the original Greek text into readable Latin. Fourteen editions, published between 1541 and 1551, contain some of the Vesalian renderings. Such progress did Vesalius make after reaching Venice that before the year was out, on the 6th of December 1537, just before his twenty-third birthday, he received the celebrated appointment from the Venetian Senate, enabling him to teach anatomy at the University of Padua.

Before his transfer to Padua, Vesalius had, doubtless in collaboration with Calcar, begun work on six anatomical plates (*Tabulae Sex*), which were printed in Venice in April of the following year (1538). They depict the portal system, the liver, kidneys and caval veins, the heart with the aorta and its branches, the skeleton in three views (front, right profile, and from behind).

The printing of these "anatomical fugitive sheets" created a great stir; a set forwarded by Andreas to his father at Court was presented to the Emperor, who praised them highly. They were plagiarized and counterfeited by Jobst de Necker, printer and publisher (1539); by Aegidius Macrolios (1539); by Walter Ryff (1541), who increased the number of figures to ten; by Johann Dryander (or Eichmann), who copied the figures in his *Anatomia Capitis Humani* (1536). Additionally, in figures of the *De Dissectione* of Charles Estienne (1545), the influence of the *Fabrica* is

Fig. 36

Fig. 37

Fig. 38

Fig. 39

Fig. 40

Fig. 41

Fig. 42

Fig. 43

Fig. 44

Figs. 36 to 44. Initial letters of intermediate size; *Fabrica*, 1555 edition. Introducing the chapters.

clearly apparent in many of the small insets; in the *De Chirurgica Institutione* of Johann Tagault (a popular book, which passed through twenty-two editions between 1543 and 1645), the Calcar figures were abominally copied.

These anatomical plates of Vesalius were designed particularly to benefit those who attended his dissections, just as the exhibitor today distributes mimeographed sheets or reprints among visitors to his booth at a state or national medical meeting.

The popularity of even such a modest set of carefully prepared figures must have encouraged Vesalius to undertake the great task of writing a complete work on human anatomy. Possessed of the enthusiasm of a zealot, Vesalius completed the *Fabrica* after three years of strenuous labor. The drawings were done by Calcar. In the same month

Fig. 45

Fig. 46

Fig. 47

Fig. 48

Fig. 49

Fig. 50

Fig. 51

Fig. 52

Fig. 53

Figs. 45 to 53. Initial letters of intermediate size continued (Figs. 45 to 52), and colophon (Fig. 53).

Vesalius finished the *Epitome* of his great work, the *Fabrica*. The plates of the *Epitome* were issued unbound; like the *Tabulae*, they were ephemeral, and hence perfect copies are excessively rare. The *Epitome* contains five plates of the musculature and figures of a nude man and woman.

Only eighteen years after the appearance of the *magnum opus*, at the age of fifty, Vesalius was drowned in a shipwreck off the island of Zante on his return from the Holy Land, where, according to rumor, he had been sent on a journey of expiation.

5. THE FABRICA OF ANDREAS VESALIUS

a. EDITIONS OF THE FABRICA

The original edition of the *Fabrica* appeared in 1543, from the press of Oporinus, in Basil. The

Fig. 54

Fig. 55

Fig. 56

Fig. 57

Fig. 58

Fig. 59

Fig. 60

Fig. 61

Fig. 62

Fig. 63

Fig. 64

Fig. 65

Fig. 66

Fig. 67

Fig. 68

Fig. 69

Figs. 54 to 69. Initial letters of small size, selected from the indices. Figures 54 to 61, from the *Fabrica*, edition of 1543; Figures 62 to 69, from the *Fabrica*, edition of 1555.

work extends over six hundred sixty-three folio pages; it is composed of seven books, and contains twenty-two full-page woodcuts and numerous smaller figures in the text.

The frontispiece shows Vesalius beginning to anatomize a female cadaver (cf. Fig. 70, from the second edition). Because methods of preservation were then unknown, removal of the organs, first to putrify, was carried out quickly. This dissection introduced the three day demonstration. In order to record his conviction that the study of anatomy should begin with the osseous framework of the body, Vesalius has the skeleton placed in a position of central importance.

Following the appearance of an unillustrated pocket edition (in Lyon, 1552), the second folio

Figs. 70 to 75. Title pages of two editions of Vesalius' *Fabrica* (Figs. 70, 71) and of anatomical treatises related thereto (Figs. 72 to 75).

Fig. 70, left. *Fabrica*, 1555 edition.
Fig. 71. *Opera Omnia* of Hermann Boerhaave and Bernhard Siegfried Albinus (1725).

edition, of eight hundred twenty-four pages, was published in Basil in 1555. This edition is said to have been lavishly prepared for; the paper was to be heavier and the type larger; the latter change necessitated the recutting of all the small initial letters so that they would equal the height of seven lines of the new type. A new block was cut for the frontispiece (Fig. 70), and the head of Vesalius was more effectively portrayed. The skeleton now carries a scythe; for concomitant exhibit of comparative anatomical features, lackeys lead a goat, as well as a dog, into the amphitheatre.

A posthumous edition of five hundred ten pages was published in Venice (1568); another of equal length followed, during the first decade of the seventeenth century (Venice, 1604).

b. CONTENTS AND TABULAE, 1555 EDITION

The edition of 1555 is regarded by many collectors as the preferred volume in this distinguished series. Each of the books, or sections, is ampler than the corresponding parts of the editio princeps. It will serve as the chief basis of the present account.

The first book, devoted to the anatomy of the bones and cartilages, covers two hundred eight folio pages. Types of cranium are figured, and the skull is shown in all effective views. The presentation of vertebral anatomy would be adequate for present-day, critical use. All flat and long bones are illustrated from every advantageous angle. The book closes with three full-page skeletal figures and as many pages of legend (Fig. 21).

The second book, dealing with the morphology of the muscles and ligaments, covers two hundred twenty-seven pages. Its text is supported by a superb set of illustrations, beginning with the musculature of the anterior surface of the body (Fig. 22). Like any of the others, these illustrations are explained by didactically clear legends, each approximately two and one-half pages in length. Several of them depict flayed figures, ingeniously displaying muscles in successive laminae.

Fig. 72. *Anatomia del Corpo Humano* of Valverde di Hamusco (1560).

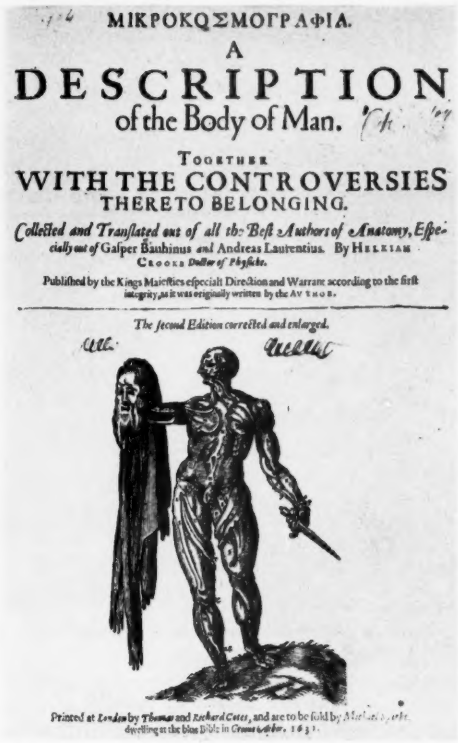
Fig. 73. *Anatomia Reformata* of Thomas Bartholin (1655).

The third book, concerned with the anatomy of veins and arteries, covers seventy pages. The figure of the portal system is particularly graphic in its display of venous channels which converge upon the liver. The treatment of the systemic veins is equally fine, the figure showing all regular segmental and axial veins together with the dural venous sinuses (Fig. 23).

In the fourth book the cranial nerves are described and figured; this section covers forty-seven pages. Particularly striking are the figures of the recurrent laryngeal nerves and the full course of the vagus, and of all the larger peripheral nerves of the body (Fig. 24). The last-named figure shows, with unusual effectiveness, the simple segmental scheme of the thoracic nerves, the cervical and the lumbosacral concentrations, and the lengthening which nerves must undergo to reach the upper and lower extremities.

The fifth book covers one hundred forty-three pages and deals with the "organs of nutrition," a category which includes the abdominal part of the alimentary tract, the urinary and reproductive organs, and the spleen. The figures are not only detailed and topographically excellent, but also attractively statuesque (cf. Fig. 87); they possess the artistic character, despite partial evisceration, of the Belvedere torso by Apollonius and of the Farnese Hercules of Glycon. Stratification is accounted for from omentum to posterior parietes. In the anatomy of the kidneys, even the capsular vessels are illustrated.

The sixth book covers fifty-seven pages and describes the heart and "servant" organs (lungs, trachea), and the pleural and pericardial investments (Fig. 25). Of paramount importance in functional theory was the nature of the septum between the cardiac ventricles. Long regarded as foraminous, for the passage of the elaborated spiritus, descriptions of this wall had been warped to fit an ancient concept of "vascular" movement. Against the influence of centuries of medical, philosophical, and ecclesiastical writing, Vesalius described the partition as he found it, that is, as an impervious interventricular wall. In the 1543 edition of the *Fabrica*, Vesalius repeated the Galenic notion that openings exist in the septum


ΜΙΚΡΟΚΟΣΜΟΓΡΑΦΙΑ.

A

DESCRIPTION

of the Body of Man.

TOGETHER

WITH THE CONTROVERSIES THERETO BELONGING.

Collected and Translated out of all the Best Authors of Anatomy, Especially out of Gasper Bauhinus *and* Andreas Laurentius. By HELKIAH CROOKE *Doctor of Physicke.*

Published by the Kings Maiesties especiall Direction and Warrant according to the first integrity, as it was originally written by the AVTHOR.

The second Edition corrected and enlarged.

Printed at *London* by *Thomas* and *Richard Cotes*, and are to be sold by *Michaell Sparke*, dwelling at the blue Bible in *Greenes Arbor*. 1631.

Fig. 74. *Description of the Body of Man*, by Helkiah Crooke (1631).

Fig. 75. The same work.

of the heart. In the second 1555 edition, Vesalius corrects the statement, saying that the septum of the heart is as dense and imperforate as the outer walls.

The seventh book extends over seventy pages, describing the brain and each meninx (Fig. 26). Cerebral divisions, ventricular spaces with contained chorioidal plexuses, dural venous sinuses, the eminences on the dorsum of the brain stem, and the basal ganglia are shown clearly in admirable illustrations.

C. INITIAL LETTERS, 1555 EDITION

Because the anatomical figures of the *Fabrica* are so utterly superior to illustrations published prior to 1543, the less obvious beauty of the decorative initial letters in the Vesalian masterpiece has captured the attention of relatively few English writers. The woodcut figures deserve appreciative comment, in introduction to which tribute their medieval lineage requires brief discussion.

In Germany, during the fifteenth century, the size, form, and style of the printed book was evolved. It was a direct descendant of the ancient manuscript. At the outset particularly it retained some of the ornamental character of the manuscript, wherein numerous border embellishments, supplementing the copied script, were employed either as pure ornaments or as scenes illustrative of the text (Fig. 27). Some were page-size, others were initial letters with pictorial background or interlaced Arabesque elements. Their history now requires a review.

In many of the books published during the sixteenth and seventeenth centuries the printers employed ornamental devices to add an attractiveness to their products which letterpress, unembellished, would fail to contribute. These initial letters, head-pieces, tail-pieces, and borders again show the intellectual vigor of a renascent world.

The earliest initials produced by mechanical means, in the printed book, appeared as early as

DE CONCEPTV
ET GENERATIONE
HOMINIS: DE MATRICE ET EIVS
PARTIBVS, NEC NON DE CONDITIONE IN-
FANTIS IN VTERO, ET GRAVIDARVM CVRA ET OFFICIO:
De partu & parturientium infantiumq; cura omnifaria: De differentijs non
naturalis partus & earundem curis: De Mola alijsq; falsis vteri tumoribus,
simulque de abortibus & monstris diuersis, nec non de conceptus signis va-
rijs: De sterilitatis causis diuersis, & de præcipuis Matricis ægritudini-
bus, omniumque horum curis varijs, libri sex, opera clarissimi viri IACOBI RVEFFI, Chirurgi Tigu-
rini, quondam congesti.
Francoforti ad Mænum. Anno M. D. LXXX.

Figs. 76 to 81. Title pages of imitative works, continued.
Fig. 76, above. *De Conceptu et Generatione Hominis* of Jacob Rueff (1580).

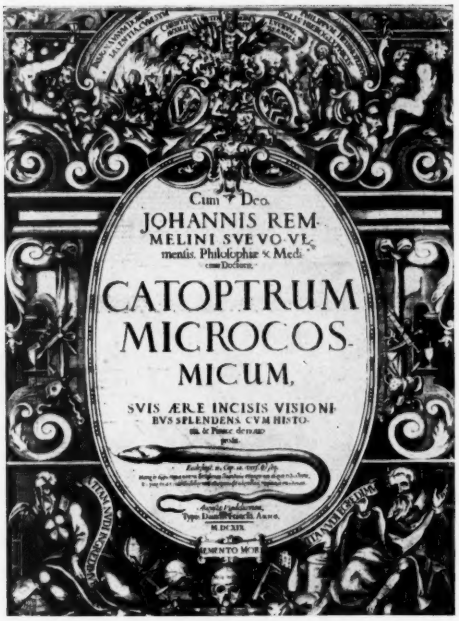


Fig. 77. *Catoptrum Microcosmicum* of Johann Remmelin (1619).

1457. During the sixteenth century, woodcut initial letters were made in profusion. By the close of the seventeenth, their employment was a rarity.

As might be expected, subjects for these various ornaments were not selected without reason; most frequently their motivation was basically religious.

Perpetuating the tradition of the early manuscript, the monumental folios of the *Fabrica* were decorated with many historical woodcut initials. These ornamental capitals depict cherubic youngsters, usually naked, who, with intent demeanor and solemn visage, act out the parts of curator, laboratory aide, male nurse, orderly, physician and surgeon. The letters B, G, J, K, U, W, X, Y, and Z are wanting in the series. Certain of these, of course, would not appear in Latin writing. The initials I, L, O, Q, T, and V are reproduced with two different backgrounds. In these six instances one of the pair of letters is of the large type (Figs. 30 to 35); all of the others are smaller, and of matching size.[1] The large blocks, 73 millimeters square, are placed at the beginning of the dedication and introduce the text of each of the seven books (Fig. 28). The letters of intermediate size, 39 by 41 millimeters, head the chapters (Fig. 29). Altogether, the initial letters appear a total of one hundred ninety-two times.[2] The

[1]For the dedication and for the seven books of the *Fabrica*, five different historiated initials are used, while three are repeated. The V (Fig. 35) introduces the dedication. Continuing in the succession, the initial O (Fig. 32) introduces liber primus (p. 1), and T (Fig. 34) serves in like capacity for liber secundus (p. 209). The initial O is repeated for liber tertius (p. 456) and T for liber quartus (p. 507). Liber quintus is introduced by title and by a main anatomical illustration of the peritoneum; the text is introduced by a repeated V (p. 589). Liber sextus is similarly arranged; the book opens with heading and illustration of the thoracic viscera, while the initial letter Q follows (p. 708) —repeated from early use in the body of the text of liber secundus (p. 255). In liber septimus, on similar plan, the book is introduced by heading and illustrations of cranial anatomy, the text, following seventeen pages later (p. 772), carrying the initial letter I (Fig. 30).

[2]In the 1555 edition the individual initial letters are employed the following number of times: A (Fig. 36), 10 times; C (Fig. 37), 15; D (Fig. 38), 10; E (Fig. 39), 8; F (Fig. 40), 5; H (Fig. 41), 9; I (Fig. 42), 18; I (Fig. 30), 1; L (Fig. 43), 10; L (Fig. 31), 1; M (Fig. 44), 9; N (Fig. 45), 3; O (Fig. 46), 7; O (Fig. 32), 2; P (Fig. 47), 17; Q (Fig. 33), 2; Q (Fig. 48), 20; R (Fig. 49), 5; S (Fig. 50), 12; T (Fig. 34), 12; T (Fig. 51), 2; V (Fig. 35), 2; V (Fig. 52), 12. In the second (1555) edition, owing to the revision of text of the first (1543) edition, some twenty replacements of initial letters (chiefly of the chapters) were made by the printer (e.g., E for O in chapter XI of book I, E for L in chapter XIII of book I).

Fig. 78. *Institutiones Anatomicae* of Caspar Bartholin (1691).

Fig. 79. *Opera*, of Ambroise Paré (Paris, 1582).

blocks, and especially those of the larger series, are believed to have been done by Calcar, who also designed the anatomical plates.

The initial letters present a full composition dealing with specific anatomical, medical, and surgical activity or with closely allied procedure or incident. The spaces behind the letters are completely filled with the composition. These decorative backgrounds fall into two simple and natural groups, namely, the preclinical and the clinical;[1] there are outdoor and indoor scenes.[2]

Considering first, the six large letters (Figs. 30 to 35), the activities therewith depicted are varied. Cherubic curators secure an anatomical specimen in letter I (Fig. 30) by robbing a grave; here, outdoors and against a background of masonry arches, the putti exhume a corpse—one holding a candle to illuminate the crypt, another keeping watch. Curiously, a soldier, present and seeming sympathetic, does not interfere with the scientific garnering of laboratory material. As background for the large initial L (Fig. 31), and in the spirit of bawdy jest, one putto draws the reader's attention to the intestinal flux of his companion, whose afternoon's adventure in hawking must wait upon certain more fundamental matters. In the initial letter O (Fig. 32), a skull is being cleaned in a cauldron which is suspended in a fireplace of ornate design; one putto works the bellows, another prepares to return the skull to the boiling pot, while a third appraises a long bone from which the soft tissues were previously removed. As a border ornament, around the oval letter, clustered leaves appear above, while griffon-like creatures give support from below. Similarly, as corner designs for the letter Q (Fig. 33), winged cherubs appear above, their wingless counterparts are busy below; one of the latter idly sharpens a dissection-instrument while the other tests the sharpness of the tail of the letter Q. In the main scene, with the letter itself, eight well nourished putti are about to carry out a cervical dissection on a pig; with the creature held to table by a chain through the mouth and rings about the legs, one

[1] The following are preclinical: Figs. 30, 32, 33, 34, 38, 43, 44, 45, 46, 47, 48, 49, 50, 51 and 52. These are clinical: Figs. 36, 37, 39, 40, 41, and 42.

[2] The following are indoor scenes: Figs. 32, 33, 40, 42, 48, and 52. These are outdoor: Figs. 30, 31, 34, 36, 37, 38, 39, 41, 43, 44, 45, 46, 47, 49, 50, and 51.

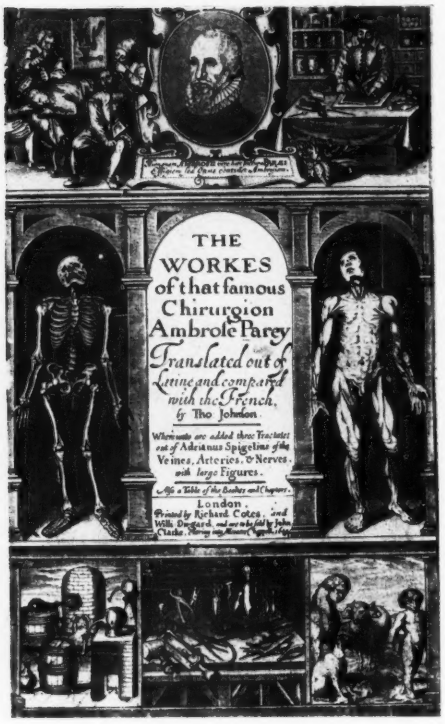


Fig. 80. *Workes*, of Paré (London, 1649).

Fig. 81. *Oeuvres*, of Paré (Lyon, 1664).

zealous putto wields the knife while a companion reads from a book of instructions. In the initial T (Fig. 34), the cross-bar of the letter serves as the crude gallows on which a pig is being elevated for evisceration.

Different from all of the other initial letters, both large and small, is the V (Fig. 35), which, first in the volume, heads the laudatory dedication to Charles V. In the highly ornamental background, between the arms of the V, Apollo and Marsyas are in contest for honors as the most skilled magician. As will be recalled, Apollo, having vanquished his opponent, thereby earns the right to do with Marsyas as he will. In the foreground, external to the V, stand the Muses (who have served as judges) on the reader's left; on the right, wearing the sash and crowned with laurel, Apollo now approaches his worsted adversary with purpose not as classical as it is anatomical.

Among the seventeen lesser letters there are scenes of clinical procedures as well as some which have to do with anatomic dissection and procurement, and with experimental study. For the letter A (Fig. 36), a corpulent putto submits to urethral exploration; he lies on a well padded bed, in the doubtful privacy of a glade. As the decorative scene for the letter C (Fig. 37), four putti transport a rack employed in the reduction of fractures; trees, hills and steepled church appear in the conventional background. The motif of the initial letter D (Fig. 38) is again anatomical; three cherubic morphologists saw open a skull, working in a spot somewhat secluded by crags and trees. The scene in the letter E (Fig. 39) is again outdoor; putti are reducing a fractured leg; one racks and pegs the injured extremity, while his colleague prepares the restraining bandage. Similar treatment is depicted in the letter F (Fig. 40), but the operation is carried out in a canopied room where the apparatus is more ambitious and, hence, less mobile; the patient sits on a low bed.

In a day of bludgeoning warfare, cranial fractures and massive contusions are common, and the frequency with which treatment is discussed and

Figs. 82 to 87. Works imitative of, or dependent upon, the *Fabrica* of Vesalius. Illustrations of the abdominal organs in the male.

Fig. 82, above. *Anatomia del Corpo Humano* of Valverde di Hamusco (1560).

Fig. 83. Pietro Berettini's *Tabulae Anatomicae* (Rome, 1741).

pictured reflects the surgeon's need for instruction. So, it is not surprising to find such a scene among the historiated initials. In the embellishment of the letter H (Fig. 41), there is shown the kind of cauterization which preceded craniotomy. The operation takes place against a background of castle and arch; the patient sits resignedly; one putto applies the iron, a second tends the fire, while two other juvenile "externes" are ready to perform less crucial tasks. Next, in alphabetical order, as a background for the letter I (Fig. 43), an urethral examination and catheterization are pictured; the quarters are opulent, the important patient considerately pillowed, yet the putti are, traditionally, naked.

In the succeeding five letters (L to P) putti either garner or study anatomical specimens (Figs. 43 to 47). For the letter L, against an austere background of unwooded hills, a corpse is lowered from a crude gallows into the arms of an avid putto (Fig. 43). One of the latter's companions holds back a company of monks, in this lesser skirmish in the mediaeval war between Science and Theology. Here the artist was obliged to build a gallows; elsewhere the cross-arm of the letter T (Fig. 51) conveniently subserved a comparable function. The letter M (Fig. 44) is less lugubriously decorated. Unlike a scene from Hamlet, the background is a cozy town; the putti, here craftily busy on the outskirts of the village, inflate the stomach of an ox. In the N (Fig. 45), they carry away a corpse for undisturbed dissection. In the initial letter O (Fig. 46) an industrious gleaner prepares to hurry away from an execution; into his wicker basket the head of the victim is being dropped—in the presence of soldiers ahorseback. For the letter P (Fig. 47) there is provided a scene depicting curator's industry: the children assemble the bones of human skeleton; at the left an extremity has been articulated, while at the right an earlier stage is represented.

In the next four letters (Q to T, Figs. 48 to 51), the activities pictured belong in the present-day

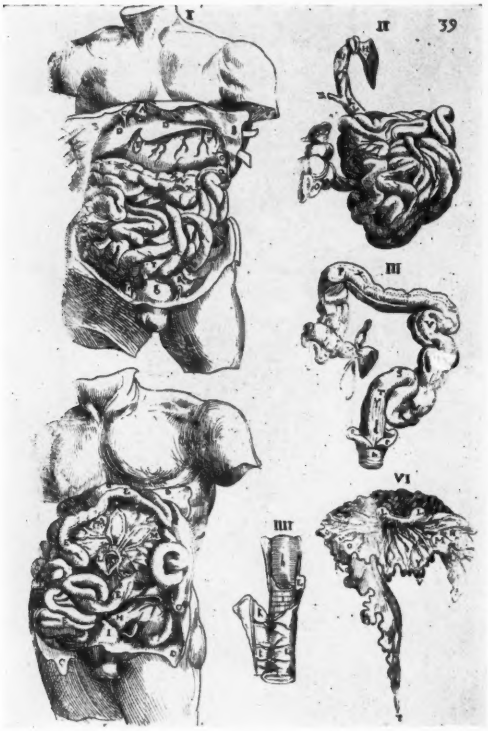


Fig. 84. Felix Plater's *De Corporis Humani Structura et Usu*, Tab. XXXIX (Basil, 1603).

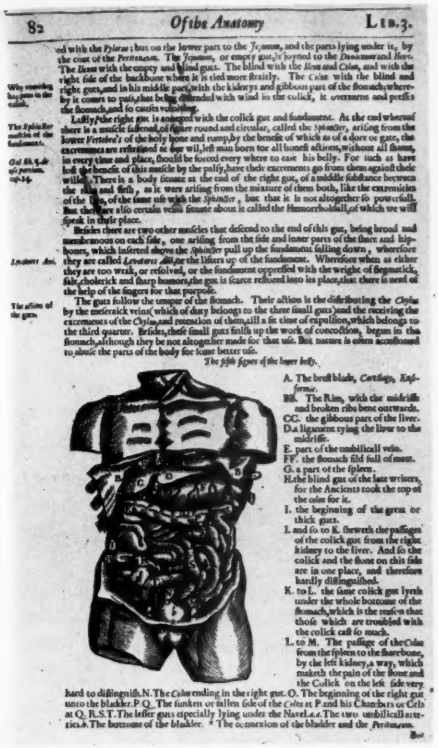
Fig. 85. Johann Remmelin's *Catoptrum Microscosmicum*, Adam figure (1619).

category of comparative anatomy. Within the medallion-space of the letter Q (Fig. 48), five putti take part in the pelvic dissection of a dog; inquisitive cherubs dissect the head of an ox, enucleating the bulb of the eye from the orbital cavity (R, Fig. 49); they bleed a dog (S, Fig. 50). For the initial letter T (Fig. 51), they string up a dog for purposes of experimentation, clubbing the helpless creature to death.

The alphabetical series closes with the letter V (Fig. 52), which portrays a venesection; a juvenile surgeon incises the skin with a lancet, to reach a vein in the cubital fossa.

The initial letters of the index make up the third series (Figs. 54 to 69). They are the smallest of the three sets, are least attractive, and bear little or no relation to the subject matter of the volume. Except for the A, they are of approximately uniform dimension (1.8 cm. square); except for the letter Z, the set employed in the first edition of the *Fabrica* (Figs. 54 to 61) was put aside in favor of another lot for the second edition (Figs. 62 to 69). Some of the blocks are remarkably clear (e.g., Figs. 54, 66, and 67); others are so poor as to require hand-lens examination (e.g., Figs. 64 and 65). Their decorative features are fabulous birds and mammals (Figs. 54 and 55), cherubic musicians (Figs. 57, 58, and 60), botanical herding and wayfaring, each finds its place in the groups (Figs. 59, 62, and 65, respectively); one putto supports the Z (Figs. 61 and 69), while another chin-rests upon the Y (Fig. 68). Assumedly these initial letters of the indices were the printer's stock in trade—ready for use in any large volume whose proportions and promise warranted their employment.

The volume closes with a highly ornamental printer's mark (Fig. 53). The colophon pictures Arion, poet and musician of ancient Greece. During a voyage at sea, the crew of the ship on which he sailed resolved to murder him for his money, and ordered him to jump overboard. Arion, having obtained permission to sing one song to the music of his cithara, threw himself into the sea. He was received miraculously on the back of a dolphin and carried safely to land. As so to Arion.



82 *Of the Anatomy* Lib. 3.

wd with the *Pylorus*; but on the lower part to the *Jejunum*, and the parts lying under it, by the coat of the *Peritonæum*. The *Jejunum*, or empty gut, is joyned to the *Duodenum* and *Ileon*. The *Ileon* with the empty and blind gut. The blind with the *Ileon* and *Colon*, and with the right side of the backbone where it is tied more straitly. The *Colon* with the blind and right gut, and in his middle part with the kidneys and gibbous part of the stomach, wherby it comers to pass, that he be distended with wind in the colick, it overturns and presses the stomach, and so causes vomiting.

Lastly, the right gut is accompted with the colick gut and fundament. As the end wherof there is a muscle fastened of figure round and circular, called the *Sphincter*, arising from the lower *Vertebra's* of the holy bone and rump, by the benefit of which as of a dore or gate, the excrements are retained at our will, left man born for all honest affaires, without all fitness, in every time and place, should be forced every where to ease his belly. For such as have lost the benefit of this muscle by the palsy, have their excrements go from them against their willes. There is a body fitnate at the end of the right gut, of a middle substance between the skin and flesh, as it were arising from the mixture of them both, like the extremities of the *Ilia*, of the same nature with the *Sphincter*, but that it is not altogether so powerfull, But therein are also certain veins fituate about it called the Hæmorrhoidall, of which we will speak in their place.

Besides there are two other muscles that defend to the end of this gut, being broad and membranous on each side, one arising from the side and inner parts of the share and hip-bones, which inserted above the *Sphincter* pull up the fundament falling down, wherefore they are called *Levatores ani*, or the lifters up of the fundament. Wherefore when as either they are too weak, or relaxed, or the fundament oppressed with the weight of fegmaticks, fals, cholericks and sharp humours, the gut is scarce reduced into its place, that there is need of the help of the fingers for that purpose.

The guts follow the temper of the stomach. Their action is the distributing the *Chylus* by the meseraick veins, (which of duty belongs to the three small guts) and the receiving the excrements of the *Chylus*, and retention of them, till a fit time of expulsion, which belongs to the third quarter. Besides, these small guts finish up the work of concoction, begun in the stomach, although they be not altogether made for that use. But nature is often accustomed to abuse the parts of the body for some better use.

The fifth figure of the lower belly.

A. The broll blade, *Cartilago, Ensiformis.*
BB. The Ribs, with the midriffe and broken ribs bent outwards.
CC. the gibbous part of the liver.
D. a ligament tying the liver to the midriffe.
E. part of the umbilicall vein.
FF. the stomach fild full of meat.
G. a part of the spleen.
H. the blind gut of the late writers, for the Ancients took the top of the colon for it.
I. the beginning of the great or thick guts.
I. and so to K. sheweth the passages of the colick gut from the right kidney to the liver. And so the colick and the stone on this side are in one place, and therefore hardly distinguished.
K. to L. the fame colick gut lyeth under the whole bottome of the stomach, which is the reason that those which are troubled with the colick cast so much.
L. to M. The passage of the *Colon* from the spleen to the share-bone, by the left kidney, a way, which maketh the pain of the bone and the Colick on the left side very hard to distinguish. N. The *Colon* ending in the right gut. O. The beginning of the right gut unto the bladder. P Q. The sunken or inlett side of the *Colon* at P and his Chamber or Cell at Q. R. S. T. The lesser guts especially lying under the Navel. a. a. The two umbilicall arteries. b. The bottome of the bladder. * The connexion of the bladder and the *Peritonæum*.

Fig. 86. *Workes of that Famous Chirurgeon Ambrose Parey*, p. 82, chap. XV of Liber 3 (1649).

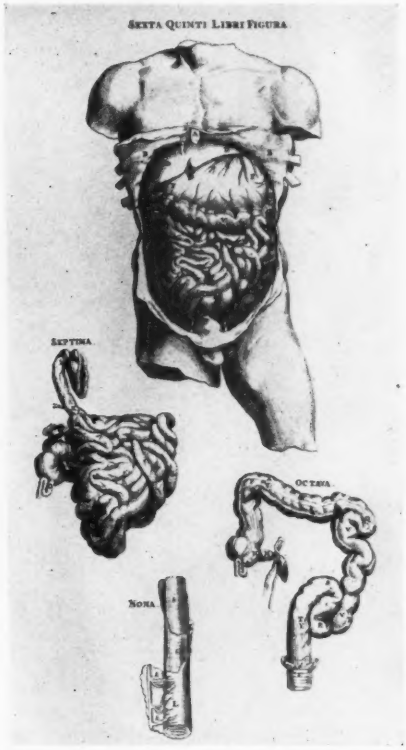


Fig. 87. *Opera Omnia* of Boerhaave and Albinus, table from fifth book.

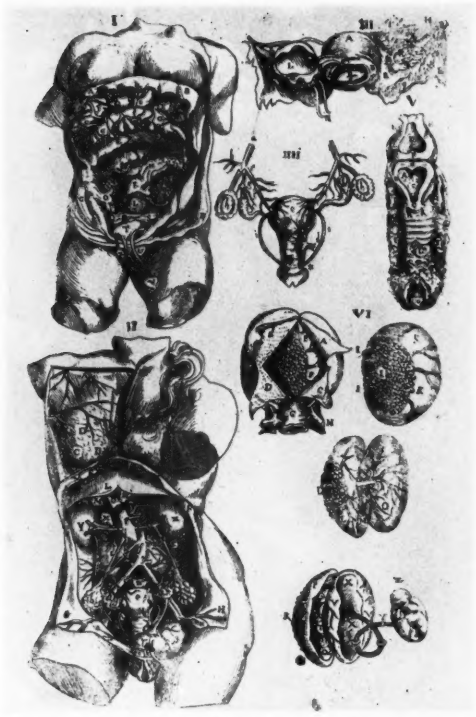
as to all intrepid men, no way is impassable; gallantry sanguineously overcomes obstacles which are barricades to the white-livered and the shoddy.

d. IMITATIVE WORKS

Emulation is tribute in its unfeigned, since most practical form; and because Andreas Vesalius became the paragon of medical authors, it is clear that Vesalius' achievements were monumental. His *Fabrica* was the source for a long succession of less original writers of textbooks in anatomy and in related medical subjects. The text was overtly borrowed, adapted, or paraphrased; the illustrations were copied in wood and copper; they were converted into superimposed sets of layers, dressed in armour or put into waggish poses; they were rarely improved, often cheapened and debased.

Perhaps the most avaricious borrowers and most unscrupulous plagiarizers of Vesalian figures were the printers of the so called "Fugitive Sheets." These broadsides were printed and distributed in large numbers during the sixteenth and the first quarter of the seventeenth centuries. By their very character and wasteful use they were predestined to be scattered, as the term "fugitive" suggests. Because of their perishable nature, very few of them have survived. Some had superimposed flaps of the various organs, but in most instances the large cuts were surrounded by smaller elements and were accompanied by a descriptive text in Latin or in the vernacular of the country. It has been said that they were displayed in barber shops, apothecary shops and even in bathhouses; that they were printed and distributed to students as abbreviated substitutes for textbooks; and they were circulated among laymen to satisfy a perennial interest in the bodily organs.

Exclusive of borrowing for the fugitive sheets, the figures of the *Epitome* and the *Fabrica* were copied by more than twenty-five authors, whose



Figs. 88 to 90. Works imitative of the *Fabrica*, continued. Illustrations of the abdominal and pelvic viscera in the female.

Fig. 88, above. From Felix Plater, Tabula XLII (1603).

Fig. 89. From Johann Remmelin, Eve figure (1619).

works passed, totally, through more than seventy-five editions (in Latin, French, Italian, Dutch, Spanish, and English).[1] Among the borrowers and imitators were Boerhaave and Albinus, Valverde, the Bartholins, Crooke, Rueff, Remmelin and Paré.[2]

Following the pattern set by Vesalius in the *Fabrica* (Fig. 70), Boerhaave and Albinus, in their *Opera Omnia*, copied the dissection scene in their title page (Fig. 71). Valverde relegated a comparable scene to the base of his ornamental page, while bringing skeletons and experimental animals into greater prominence (Fig. 72). Thomas Bartholin employed a full human hide to make an arresting title page (Fig. 73). Crooke employed a similar device, but caused the stripped muscleman to hold his own skin and the instrument used in removing it (Fig. 74). Crooke also copied Vesalius' plan but added lesser scenes of surgical, biblical and moralistic character (Fig. 75). Rueff introduced his midwifery with a title page which depicts a birth-chamber, complete with attentive nurses, hungry dog and bibulous servants (Fig. 76). Remmelin pictured scholars and the accouterments of knowledge (Fig. 77); Caspar Bartholin exhibited the figures of the medically great—including, of course, Vesalius (Fig. 78). Paré's title pages cover various subjects (Figs. 79 to 81), the most appropriate being that which appeared in the English edition of 1649 (Fig. 80).

Only when Calcar's drawings are compared with those in the *sequelae* does the full quality of the former become apparent. Two brief visceral sets (Figs. 82 to 87, and Figs. 88 to 90) demonstrate the excellence of the Vesalian illustration.

[1] Among the authors of sequelae, the following have been named by authorities: Maschenbauer; Leveling, Raynald; Geminus; Jaudin; Bauman; Boerhaave and Albinus; Bonavera; Botter; Fontanus; Fuchs; Van de Gracht; Moro and Montani; Paauw; Plater; Sandifort; Torteblat; Valverde; Paré; Bartholin; Remmelinus; Crooke.

[2] In Dr. Harvey Cushing's scholarly volume, *A Bio-bibliography of Andreas Vesalius* (New York: Schuman's, 1943), the illustrations and text of the several editions of the *Fabrica*, and of its antecedents and *sequelae*, are fully discussed.

As its title indicates, the treatise contains a bibliography of Vesaliana (451 items) and an authoritative biography, whose portions are chronologically arranged in relation to Vesalius' preparation and publication of his anatomic work.

Juan de Valverde, in his anatomical plates, put the muscle-men to work. In one figure a brawny manikin holds suspended his own cutaneous coat; upright anatomical subjects draw aside the flaps of the abdominal wall with their own hands and lift the omental apron with their teeth, better to display their guts to the barber-surgeons of Seville. Not content with demonstrations of interior structures, Valverde dressed some of his subjects in partial armour, perhaps as a concession to the military trend of Spain's ambitions (Fig. 82).

Berettini regrouped the pictorial material, to combine, in each of several plates, myological, nervous, and visceral elements; in one instance, figures of the intestines and stomach appear as bas-reliefs on block-like pedestals, while the flayed muscle-man holds a framed figure of a cervical dissection (Fig. 83). Rueff limited his borrowing to illustrations of female pelvic anatomy (Fig. 90). Plater adhered rather closely to the Vesalian arrangement of figures (Figs. 84 and 88), as did Boerhaave and Albinus (Fig. 87); both Remmelin and Paré altered the schema very considerably (Figs. 85, 86, and 89). Because of the ingenuity exercised in the preparation of Remmelin's *Tabulae*, and the popularity of Paré's commonplace figures, the works of these writers call for special comment.

Of all the copied forms of the Vesalian *Fabrica*, that by Johann Remmelin displays the most ingenious craftsmanship. Remmelin, a physician of Ulm, artfully arranged the anatomical structures of the human body on plates in such a manner that parts lying at successively deeper levels were shown by means of pictures fastened one to the other like the pages of a book. These pages were published in 1613 under the title *Catoptron Microcosmicum*. In this set of plates man (Fig. 85) or woman (Fig. 89) could view his microscosmic parts as if in a "mirror." The figures were frank copies of those in the *Fabrica*.

In the collected *Workes* of Ambroise Paré, descriptive material and figures were used, without notable replacement, through thirteen French editions, a Latin, and several English editions. The first edition (French) appeared in 1575, in Paré's sixty-fifth year. Editions succeeded each other in uninterrupted succession, to the thirteenth in 1685. Since the volume of collected *Workes* was a medicosurgical encyclopedia, its appeal was exceptionally wide. In being part of such a popular tome, the subject matter of the Vesalian *Tabulae*, debased to the status of figures in the text, was destined to be spread to every land where the influence of European medicine was felt. Anatomy was but a small part of Paré's encyclopedic volume. He discussed dislocations and luxations, means of supplying an artificial nose, ivory teeth held in place by strings, a plate to fill a defect in the palate. He discussed the unicorn and opposed its use as an antidote against poisons, told eyewitness stories of plague-ridden towns, described monsters and prodigies, gout and the French pox, quackery, conception, birth, and the embalming of the dead.

Fig. 90. Jacob Rueff, *De Conceptu et Generatione Hominis*, second book (1580).

6. GENERAL CONSIDERATIONS

In the 1555 edition of the *Fabrica*, as in the 1543, or first edition, ornamentation is lavish; the muscular figures stand effectively against old-world backgrounds, whose elements are the familiar bridges, rivers, and thatched houses of the Paduan environs; the superabundant initial letters are varied, their scenes pertinent; the title page, displaying a dissection scene in an amphitheatre of unexpected grandeur, is an exceptionally attractive introductory piece.

None of the imitative works equalled the *Fabrica* in respect to pictorial engraving. In Creigher's edition of the *Fabrica*, published in Venice in 1568, ornamental backgrounds are omitted; the muscle-men stand merely on plots of sparsely vegetate earth. The initial letters, poorly executed, are employed to head the chapters; they hold no relevancy to the text, being arabesques of conventional design (cf. Figs. 66 and 67). In the magnificent two-volume folios of Boerhaave and Albinus, published in 1725, for which Jan Wandelaer engraved the *Tabulae* in copper, the dissection-scene appears to particular advantage, as does also the likeness of Vesalius (frontispiece). In the grand full-page figures of the muscle-men, the backgrounds are retained; walled towns, tidy villages, winding paths, meandering rivers, hills and glades, austere mountains, mossy glens and Roman columns, stone bridges and ancient gates, lend such naturalness to the anatomic portraiture that the presence of a gracefully ambulatory specimen seems neither lugubrious nor doleful. Yet, despite the meticulous borrowing of the landscapes, the initial letters, used in all of the chapters of the several books, are merely flowered compositions; the pertinency which characterized the letters in Vesalius' works was sacrificed in the copied versions. Tailpieces, likewise irrelevant to the text material, are repetitiously employed.

In the work of Valverde (1560) the backgrounds are omitted; the muscle-men stand upon plots of hummocky, tufted ground. Initial letters appear in several of the full-page legends (facing the plates of illustrations); they are sparingly used in the text, to introduce each of the seven books; the chapters carry no initial letters. The chapter letters represent mariner, warrior, armorer, fabulous beast, and Neptune astride his sea calves—all in keeping with Valverde's martial display of the visceral specimen, clad in hauberk.

In the anatomies of Crooke and Paré, the title pages are distinctly ornamental. However, as in Valverde's volume, backgrounds are wanting. Initial letters are profusely used; introducing chapters, they match the *Fabrica* in their profusion. However, they are small arabesques of the kind which might have been available in any busy printery. Headpieces and tailpieces, like the initial letters, bear no relation to the subject matter of the volumes.

In all respects, then, the *Fabrica* is an epochal work; as has been shown, the volume promptly became the repository, textual and pictorial, from which medical writers, less judicious, assiduous and ingenious than Andreas Vesalius, drew wholesale, or, like gleaners, took impatient and fragmentary excerpts. The greatness of the source is attested to by the inability of many of the copyists to maintain the standard set by the original work. Vesalius' *Fabrica* enjoyed the advantages offered by a volume of folio dimensions; his drawings were not required to take shocking reduction. The presswork was excellent, the engraved figures being superior to many reproduced by similar techniques in our own day. The collecting of Vesaliana long ago became a rewarding avocation among the world's medically great. The *Fabrica*, which is now complacently in the fifth century of its existence, is the pre-eminent nucleus for either a personal or institutional library of medical history.

Certainly the embellishment of the *Fabrica*, in the form of title page, historiated initial letters and ornamental background, adds greatly to its bibliophilic charm. The attractive initial letters record the interests and extramural occupations of the anatomist and the surgeon. In handling these subjects, the forbidding and the lugubrious aspects of professional endeavor are converted into pictorial witticisms—the latter note serving as a foil to set off the directly pedagogic objectives of the writer. In shunning the service that such decorations might perform for our modern textbooks, we have lost an opportunity to be subtly instructive and, at the same time, delicately appreciative of the humor of our faithful artists. Nurturing the misconception that scholarship ceases to be impressive when it is no longer stodgily sedate, we persistently fail to employ a device which sweetens textual fodder and supplies the surfeited reader with the alimental juice of whimsey.

REVIEWS OF NEW BOOKS

THE first volume has been published of a series of books to be devoted to various methods and techniques used for experimental purposes. The governing board, consisting of Irvine H. Page, A. C. Ivy, Coltin H. MacLeod, Carl F. Schmidt, and David L. Thomson, state in the preface 4 reasons for this series of books: first, to give an appraisal and discussion of the various methods that have been proposed for experimental problems; second, to give a detailed description of methods; third, to give useful modifications of methods that are difficult to find in the literature; fourth, to make available many methods that were developed during the war and which have been described only in official reports. Each volume of *Methods in Medical Research*[1] will be divided into 4 or 5 principal sections, each of which shall, for that volume, represent one of the broad fields of medical research: biochemistry, physiology, pharmacology, microbiology, immunology, and biophysics including radiobiology. From these broad fields, various topics will be discussed by experts in that particular field.

The first volume is divided into 4 sections. Section 1, edited by Henry Welch, deals with the assay of antibiotics—penicillin, streptomycin, tyrothricin, bacitracin; it also includes tests for pyrogens, toxicity, and sterility of penicillin and streptomycin solutions and the histamine content of streptomycin. Section 2, edited by Harold D. Green, is concerned with apparatus and methods for the study of blood flow measurement in the circulation; such as, venous drainage recorders, mean flow recorders, pulsatile flow meters, perfusion systems, indirect methods for regional blood flow, collateral circulation, cardiac output and contractility, and cardiovascular activity. Section 3, edited by A. C. Ivy, concerns selected methods in gastroenterologic research including the assay of choleretic compounds, the preparation and use of the Mann-Williamson dog, and the study of gastric acidity in man. Section 4, edited by Van R. Potter, contains methods for the study of cellular respiration by means of measuring the respiration of intact animals and tissue slices by the homogenate technique, and by the analyses of tissue metabolites with *in situ* freezing techniques.

The book consists of 357 pages, it is well illustrated and contains many references. There are 2 indices, one for subject matter and the other of names cited throughout the book. It is an excellent source of information for anyone engaged in research work and will save a great deal of time in the development of a research problem. After the whole series is completed, the governing board may consider publishing a volume each year dealing with the newer methods in all branches of biological research.

OPAL E. HEPLER.

[1]METHODS IN MEDICAL RESEARCH. Van R. Potter, Ph.D., Editor in Chief, Vol 1. Chicago: The Year Book Publishers, Inc. 1948.

THE present accumulation of morphological, physiological, and clinical knowledge of each portion of the human body is now great, and almost beyond the comprehension of an individual student or of a practitioner in any single branch of medicine. This is specially true of the head, in which territory the general surgeon, the neurosurgeon and his colleagues in maxillofacial reconstruction, the otolaryngologist, the opthalmologist, and the anesthetist find urgent demand for more precise and more dependable knowledge. Admittedly, this wealth of material often appears forbidding to the practitioner who desires to review the anatomy of the head and neck, and to the beginning student who may be preparing for a clinical specialty. For either, anatomic architecture must be regarded as basic.

The *Detailed Atlas of the Head and Neck*[1] offers the needed pictorial guidance. So complete is the series of pictures that it may safely be employed to replace the lesser sets of diagrammatized figures which have become the familiar, sometimes misleading, stock-in-trade of the specialist's library. Surface landmarks are emphasized, successively deeper anatomical layers and groups of structures are rationally portrayed, interrelationships are clarified. Not only are series of frontal and transverse sections through the most critical surgical levels included, but, in addition, regional dissections are abundantly illustrated; this combination facilitates the reader's acquirement of a serviceable appreciation of orientation and depth.

As. Dr. E. A. Boyden points out in the deservedly laudatory introduction, the drawings in this fine work by Truex and Kellner were all made directly from original regional dissections, the same specimen being used in depicting the anatomy of each series. In order to insure the retention of proper proportions, either scaled enlargements or life-sized drawings were made. The illustrations in each series were uniformly reduced in publication; numerals, which accompany each figure, record the positive proportion to life size. The figures represent serial dissections from superficial to more deeply situated layers, and thus preserve a continuity, from one plate to the next, of the important structures within each region. This logical scheme not only permits visualization of the laminar relationships of fascia, muscles, bones, vessels, and nerves at each of the major cervical and facial levels, but also allows ready

[1]DETAILED ATLAS OF THE HEAD AND NECK. By Raymond C. Truex, M.S., Ph.D., and Carl E. Kellner. New York: Oxford University Press, 1948.

review of the structures traversed, displaced, or excised in the course of the regional dissection. This method has been consistently followed for the anatomy of the neck, face, brain and spinal cord, orbit, ear, pharynx, mouth, larynx, nose, and paranasal sinuses. Additionally, axilla and thorax are handled with sufficient detail to demonstrate the continuity of the cervical organs, vessels, and nerves into the former regions.

Altogether, this volume must be hailed as exceptionally useful; its illustrations portray human structures as they are actually found in dissected and sectioned specimens, not as conveniently idealized or otherwise altered to match stereotyped illustrations of antecedent textbooks. It presents the kind of information which the present-day surgeon needs, and to the possession of which the medical student should early be introduced.

BARRY ANSON.

IN the 11 years since Dr. Means published the first edition of his book, *The Thyroid and Its Diseases*,[1] a mass of new knowledge about the thyroid gland has been accumulated. Most of this knowledge is in the field of thyroid physiology and has been gained through the use of two new tools: (1) the antithyroid drugs, and (2) radioiodine. In spite of the overwhelming amount and complexity of the work with these agents, Dr. Means and his collaborators have not enlarged the new edition to any extent. The new material has been assimilated and presented in its rightful place as a part of the whole thyroid picture.

As in the first edition, the writing is simple and straightforward. Many case histories are given to illustrate special points. Charts and graphs are liberally used. The approach throughout is mainly physiologic, yet the clinical picture is clearly set forth, and understanding of it is enhanced by the presentation of the physiologic basis. The completeness of the book has been furthered by the addition of chapters on pathology and tumors by Dr. R. W. Rawson, and on surgery by Dr. Oliver Cope. Dr. Cope's chapter is detailed and contains many practical points for the thyroid surgeon.

The book is divided in much the same way as was the previous edition. The chapter which in the first edition was called "Simple Goiter" is now entitled "Goiters Due Primarily to Extrinsic Causes." Studies on radioiodine and on the goitrogens have pointed out the complexity of this group of thyroid disorders, and Dr. Means has wisely dropped the term "simple" from his classification. The chapter formerly titled "Toxic Goiter" is now called "Graves' Disease" and a separate heading is given to adenomatous goiter with hyperthyroidism. Very little is said in the second edition about total thyroidectomy as a treatment for other diseases; a chapter was devoted to this subject in the first edition. "Nodular Goiter" and "Malignant Goiter" have now been combined into a single chapter entitled "Tumors of the Thyroid." It is interesting also to compare the final chapter "Fact and Fancy in Matters Thyroid" in the two editions. Some questions raised in this discussion 11 years ago have been answered in full or in part, but they have been replaced, as usual, by further questions. The emphasis in the later edition is on physiology and relation of the thyroid to the body as a whole.

This volume is a stimulating dissertation. Each chapter in the book is followed by a concise summary and an inclusive bibliography. The index is excellent. A word of thanks should be given to the publishers for the improvement of the format of this edition over the previous one. As Dr. Cope points out, "The surgeon who operates on the thyroid must have special knowledge of the gland, its action, diseases and environment." This statement holds true for anyone who undertakes the diagnosis and treatment of diseases of the thyroid. Dr. Means' book contains this special knowledge.

W. M. BALFOUR.

THE volume, *Acute Intestinal Obstruction*,[2] is an easily readable 259 page book intended to acquaint the well trained surgeon with the known facts concerning gastrointestinal obstruction between the duodenum and the anus. A broad and very well documented review of the physiological aspects is exceptionally well done. For a work so well founded in the older literature on this subject there is unfortunately a none too strong survey of the physiological and therapeutic developments of the past few years.

There is a reference list of some 350 titles, 2 being case reports of the author's. Rather free reference to many of the workers listed in the bibliography is made, but there is considerable ambiguity in the text as to the origins of the techniques described. Procedures are included which have been abandoned by most students of the subject, and some of the recent excellent contributions are not yet included.

This is a very informative book for the casual reader, and a thought-provoking one for the thoroughly experienced surgeon. The shortcomings indicated above, however, unfortunately render it an incomplete guide in the training of the abdominal surgeon.

CLARENCE DENNIS.

THE new American text *Bacterial and Mycotic Infections of Man*[3] is published as a companion volume to Rivers' edition of *Virus and Rickettsial Infections*. There are 34 contributors to the 37 chapters. All of the authors are acknowledged leaders in

[1] THE THYROID AND ITS DISEASES. By J. H. Means, M.D. 2d ed. Philadelphia, London, and Montreal: J. B. Lippincott Co., 1948.

[2] ACUTE INTESTINAL OBSTRUCTION. By Rodney Smith, M.S., F.R.C.S. With a chapter on radiological diagnosis by Eric Samuel, M.D., F.R.C.S., F.F.R., D.M.R.E. Foreword by Rupert Vaughan Hudson, F.R.C.S. Baltimore: The Williams & Wilkins Co., 1948.

[3] BACTERIAL AND MYCOTIC INFECTIONS OF MAN. Edited by René J. Dubos, Ph.D. Philadelphia, London, and Montreal: J. B. Lippincott Co., 1948.

their chosen field of fundamental research. Each of the chapters presents a precise summary of current investigation in a way that is possible only under the plan of group authorship.

The opening chapters are devoted to an exposition of host-parasite relationships, bacterial morphology and physiology, and the principles of immunity and allergy. Especially outstanding are the sections on bacterial morphology and physiology by Dubos and Pappenheimer and on the allergic state by Chase.

Excellent coverage is given to the bacteria of proved or probable pathogenicity to man. Adherence to the taxonomy adopted in the latest edition of Bergey's *Manual* represents a forward step for clinical bacteriology to follow. Homer Swift's section on the streptococci is excellent, as is Blair's handling of the staphylococci, and Mueller's discussion of diphtheria. The completeness of this portion of the book may be emphasized by reference to the splendid summary of the current studies upon Streptobacillus moniliformis and the pleuropneumonia group by Sabin.

The precedent set by Hiss and Zinsser for inclusion of chapters on mycotic infections in bacteriologic texts has been adopted. Conant's sections on the actinomycetes and the fungi imperfecti are concise and clear. Separate handling of the Wolff-Israel bacillus and the nocardia follows American custom and clinical practice.

The concluding chapters embrace a variety of subjects including the technique of bacterial identification, principles of sterilization, and a brief résumé of antibiotic and chemotherapeutic agents. One feels that limited space was assigned to these subjects to gain complete textual coverage. The compromise which has been made is disappointing. Another criticism of the text is the brevity of the sections on the clostridia.

The book is to be regarded as a valuable and thoroughly up-to-date review of academic and investigative bacteriology. It has all the qualifications of a text for students of bacteriology and should appeal to the clinician as a reference in the thoughtful contemplation of clinical problems in specific infections.

CHAMP LYONS.

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgment must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

FACTS ABOUT THE CHANGE OF LIFE. By E. C. Hamblen, M.D., F.A.C.S. Springfield, Ill.: Charles C Thomas, 1949.

FOOD AND FACTS FOR THE DIABETIC. By Joseph H. Barach, M.D., F.A.C.P. New York: Oxford University Press, 1949.

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CLINICAL CONGRESS OF AMERICAN COLLEGE OF SURGEONS

DALLAS B. PHEMISTER, Chicago, *President*
FREDERICK A. COLLER, Ann Arbor, *President-Elect*

PRELIMINARY PROGRAM FOR THE 35th CLINICAL CONGRESS—THE STEVENS, CHICAGO, OCTOBER 17 TO 21, 1949

WITH hotel headquarters at The Stevens, the thirty-fifth Clinical Congress of the American College of Surgeons will be held in Chicago from October 17 to 21, 1949. On the last day, October 21, the Sixth Inter-American Congress of Surgery, for which the Clinical Congress will be host, will open a three-day series of sessions. The plans for the Inter-American Congress are described in a separate article. The American College of Surgeons is a member of the Association of Inter-American Congresses of Surgery.

Operative and nonoperative clinics will be held in some twenty hospitals in the Chicago area each day during the Clinical Congress. The hospitals which will participate in the clinical program are approved by the American College of Surgeons for graduate training in surgery. The schedule of clinics, which will cover general surgery, obstetrics and gynecology, fractures and other traumas, orthopedic surgery, thoracic surgery, neurosurgery, genitourinary surgery, and ophthalmology and otorhinolaryngology, will be published in a *Daily Clinical Bulletin* which will be issued each day during the Clinical Congress. The clinic schedules will also be posted on bulletin boards.

Operations will be telecast, in color, to the hotel from one or more of the hospitals at scheduled periods each day. The successful demonstrations of television at the Clinical Congress in New York in 1947, and at the Clinical Congress in Los Angeles in 1948, make it highly desirable to continue the use of this medium. Television has proved itself to be an ideal means of furthering the "Show me" purpose which was the main incentive for the founding of the Clinical Congress of Surgeons of North America in 1910, three years before the American College of Surgeons was organized. That first Clinical Congress was held in Chicago. The 1949 meeting will be the ninth held in that city.

A varied and comprehensive program of meetings will be held at the headquarters hotel. A general assembly for both surgeons and hospital personnel will be the opening session on Monday morning, October 17. Scientific sessions, official meetings, hospital conferences, showings of medical motion pictures, and telecasts will follow during the five days, and many surgeons will undoubtedly wish to remain for the sessions of the Sixth Inter-American Congress of Surgery on Saturday and Sunday. Delegates and visitors to the latter meeting will likewise be welcome at clinics and other sessions of the Clinical Congress of the American College of Surgeons. All will be interested in the extensive display of technical exhibits in the exhibition hall on the lower level and in the scientific exhibit on the mezzanine floor of the hotel.

PRESIDENTIAL MEETING

The Presidential Meeting will be held on Monday evening, October 17. At this meeting the officers-elect, consisting of Dr. Frederick A. Coller of Ann Arbor, president, Dr. Donald G. Tollefson of Los Angeles, first vice-president, and Dr. Robert M. Moore of Galveston, second vice-president, will be installed. The outgoing president, Dr. Dallas B. Phemister of Chicago, will preside and will deliver the Presidential Address.

Sir James R. Learmonth of Edinburgh will deliver the fourth Martin Memorial Lecture. His subject will be "Collateral Circulations, Natural and Artificial."

CONVOCATION

The formal initiation ceremonies for the new Fellows will be a colorful feature of the annual Convocation which will be held on the final evening, Friday, October 21. Honorary fellowships

will also be conferred on this occasion. Lord Webb-Johnson of London, president of the Royal College of Surgeons, will deliver the Fellowship Address.

EVENING SCIENTIFIC SESSIONS—GENERAL SURGERY

The program and speakers for the Tuesday evening general surgery session will be as follows:

Symposium—Acute Surgical Emergencies in Gynecology and Obstetrics:

- General Introduction. NEWELL W. PHILPOTT, M.D., F.A.C.S., Montreal.
- Tubal Pregnancy, Its Diagnosis and Treatment. LEWIS C. SCHEFFEY, M.D., Philadelphia.
- Pelvic Peritonitis Occurring in the Obstetrical or Gynecological Patient. FRANK GLENN, M.D., F.A.C.S., New York.
- Emergency Cesarean Section. WILLIAM E. STUDDIFORD, M.D., F.A.C.S., New York.

The program and speakers for the Wednesday evening general surgery session will be as follows:

Fracture Oration. Fracture Hazards OTTO J. HERMANN, M.D., F.A.C.S., Boston

Symposium—Blood Coagulation and the use of Anticoagulants:

- The Significance of Different Methods for Prothrombin Estimation and their Relative Values. JOHN H. OLWIN, M.D., Chicago.
- Studies on Antithrombin and Etiologic Factors in Phlebothrombosis. JOHN H. KAY, M.D., New Orleans.
- A Further Report on Dicumarol Prophylaxis against Venous Thrombosis in Women Undergoing Surgery. GEORGE VAN S. SMITH, M. D., F.A.C.S., Brookline, Massachusetts.

The program and speakers for the Thursday evening general surgery session will be as follows:

Symposium—Malignant Disease:

- Chemotherapy in Malignant Neoplastic Disease. CARL V. MOORE, M.D., St. Louis.
- Hormone Therapy of Cancer. CHARLES B. HUGGINS, M.D., Chicago.
- The Use of Radioactive Iodine in Studying the Pathologic Physiology of Thyroid Cancer. RULON W. RAWSON, M.D., New York.
- What We have Learned from Isotopes Concerning Depletion and Repair in Surgical Patients. FRANCIS D. MOORE, M.D., F.A.C.S., Boston.

GENERAL SURGERY PANEL DISCUSSIONS

General surgery panel discussions will be held on Monday, Tuesday, and Wednesday afternoons, from 1:30 to 3:00 and from 3:30 to 5:00 o'clock. The subjects and the names of the moderators follow:

Monday—1:30 to 3:00 p.m.

Surgical Lesions of the Breast. GEORGE G. FINNEY, M.D., F.A.C.S., Baltimore.

3:30 to 5:00 p.m.

Fractures of the Skull. ELDRIDGE H. CAMPBELL, M.D., F.A.C.S., Albany.

Tuesday—1:30 to 3:00 p.m.

Massive Upper Abdominal Hemorrhage. JOHN H. MULHOLLAND, M.D., F.A.C.S., New York.

3:30 to 5:00 p.m.

New Surgical Technique in Drug Treated Infections. CHAMP LYONS, M.D., New Orleans.

Wednesday—1:30 to 3:00 p.m.

The Management of Acute Emergencies Occurring During Operations. I. MIMS GAGE, M.D., F.A.C.S., New Orleans.

3:30 to 5:00 p.m.

Preoperative and Postoperative Care and Anesthesia for Infants. THOMAS H. LANMAN, M.D., F.A.C.S., Boston.

SPECIALTY SESSIONS

Plans will be announced later for the sessions in ophthalmology, otorhinolaryngology, orthopedic surgery, plastic surgery, urology, thoracic surgery, neurological surgery, and obstetrics and gynecology. Friday afternoon will be devoted to panel discussions in the surgical specialties, but a definite schedule has not yet been completed for other sessions.

FORUM ON FUNDAMENTAL SURGICAL PROBLEMS

The Forum on Fundamental Surgical Problems will be held on Monday through Thursday afternoons, and Tuesday through Friday mornings. Brief reports of original clinical and experimental observations relating to the broad aspects of surgery and the surgical specialties will be presented, under the general direction of Dr. Owen H. Wangensteen, chairman of the committee, Forum on Fundamental Surgical Problems.

HOSPITAL CONFERENCES

The twenty-eighth Hospital Standardization Conference will be held during the first 4 days of the Clinical Congress. Its opening meeting will constitute the first formal session of the Clinical

Congress and will be for both surgeons and hospital representatives. Dr. Dallas B. Phemister, president of the College, will preside.

Hospital administrators, trustees, members of medical staffs, nurses, technicians, dietitians, and heads of the various hospital departments and their personnel, are invited to participate in the discussions at the hospital conferences which will be directed by leading authorities in the hospital field in the United States and Canada. The program will include formal sessions, panel discussions, round table conferences, symposia, and forums.

COMMITTEE ON ARRANGEMENTS AND EXECUTIVE COMMITTEE

The Chicago Committee on Arrangements and Executive Committee for the Clinical Congress are actively at work on arrangements for the program. The membership of these Committees follows:

Committee on Arrangements

Warren H. Cole, M.D., F.A.C.S., Chairman
Lester R. Dragstedt, M.D., F.A.C.S., Vice Chairman
Michael L. Mason, M.D. F.A.C.S., Secretary
Dallas B. Phemister, M.D., F.A.C.S., President and Regent of the College
William E. Adams, M.D., F.A.C.S.
James J. Callahan, M.D., F.A.C.S.
Fremont A. Chandler, M.D., F.A.C.S.
Edward A. Christofferson, M.D., F.A.C.S.
Vernon C. David, M.D., F.A.C.S.
Loyal Davis, M.D., F.A.C.S.
M. Edward Davis, M.D., F.A.C.S.
Paul W. Greeley, M.D., F.A.C.S.
Paul H. Holinger, M.D., F.A.C.S.
Sumner L. Koch, M.D., F.A.C.S.
Herman L. Kretschmer, M.D., F.A.C.S.
Walter G. Maddock, M.D., F.A.C.S.
Foster L. McMillan, M.D., F.A.C.S.
Karl A. Meyer, M.D., F.A.C.S.
Harry A. Oberhelman, M.D., F.A.C.S.
Willis J. Potts, M.D., F.A.C.S.
Charles B. Puestow, M.D., F.A.C.S.
Herbert E. Schmitz, M.D., F.A.C.S.
Derrick T. Vail, M.D., F.A.C.S.

EXECUTIVE COMMITTEE

Warren H. Cole, M.D., Chairman
Lester R. Dragstedt, M.D., Vice Chairman
Michael L. Mason, M.D., Secretary
Dallas B. Phemister, M.D., President and Regent of the College
James J. Callahan, M.D.
Loyal Davis, M.D.
Walter G. Maddock, M.D

GENERAL AND PROGRAM COMMITTEES

The Clinical Congress general committee which operates under the Administrative Board of the College, consists of Dr. Malcolm T. MacEachern, chairman, Miss Eleanor K. Grimm, secretary, Doctors Bowman C. Crowell, Charles F. Branch, George H. Miller and H. Prather Saunders, and Mr. Edward G. Sandrok, Mr. James S. Shannon, and Miss Laura G. Jackson.

The Clinical Congress Committee on Program consists of Dr. Frederick A. Coller, chairman, and Doctors Henry W. Cave, Evarts A. Graham, and Alton Ochsner.

The Advisory Committee on Programs consists of Dr. George H. Miller, chairman, and Doctors Warren H. Cole, Sumner L. Koch, Michael L. Mason, Charles B. Puestow, Bowman C. Crowell, H. Prather Saunders, Charles F. Branch, and Malcolm T. MacEachern.

MEDICAL MOTION PICTURES

The showing of medical motion pictures each day will again be a popular feature of the Clinical Congress. The latest available films on surgery and related subjects will be presented. Special showings will be arranged of medical motion pictures in the fields of ophthalmology and otorhinolaryngology. Both sound and silent films will be shown, all of which will have been approved by the Committee on Motion Pictures.

Some of the newer medical motion pictures which have been or are being produced under Directing Committees of the College, will be presented during the Clinical Congress. Among these will be the film entitled "Injuries of the Peripheral Nerves" directed by Dr. Loyal Davis, under a grant from the Johnson & Johnson Research Foundation. A première showing of this particular film will take place in the Murphy Memorial Auditorium of the College at the time of the Congress in October.

TECHNICAL AND EDUCATIONAL EXHIBITION

The Technical and Educational Exhibits will be held in the Exhibition Hall on the lower level of The Stevens. There will be represented leading manufacturers of surgical instruments, of x-ray apparatus, of sterilizers, of operating room lights, of ligatures, of dressings, of hospital apparatus and supplies of all kinds, and of pharmaceuticals, and publishers of medical books.

There will also be presented exhibits depicting the work of the College.

ADVANCE REGISTRATION

Surgeons who wish to attend the Congress should register in advance. Advance registration will greatly expedite the procedure of registering. No registration fee will be charged Fellows whose dues are paid to December 31, 1948. For endorsed Junior and Senior Candidates, the fee will be $5.00. Non-Fellows who after individual consideration are permitted to register, will pay a fee of $10.00. No registration fee will be required of initiates of the class of 1949.

HOTEL RESERVATIONS

It is desirable to make hotel reservations as early as possible. In making these, communications should be addressed to the Convention Housing Bureau, 105 West Madison Street, Chicago, stating that you will be attending the Clinical Congress of the American College of Surgeons. All hotel reservations, both for surgeons and hospital representatives, are to clear through this Bureau. No correspondence should be sent directly to the hotels. A form for reservations was enclosed in the letter recently sent to Fellows. Choice of hotels may be designated.

A list of the principal participating hotels and minimum rates follows:

Chicago Hotels	Single	Double
Atlantic	$3.50	$5.00
Bismarck	5.00	8.00
Brevoort	3.50	6.00
Chicagoan	3.75	5.50
Drake	4.50	7.50
Eastgate	3.50	5.50
Hamilton	4.00	6.00
Harrison	3.00	4.00
Knickerbocker	5.00	8.00
Maryland	4.00	6.00
Midland	3.00	4.50
Palmer House	4.00	8.00
Sheraton	3.85	6.40
Stevens	4.50	7.00

SIXTH INTER-AMERICAN CONGRESS OF SURGERY

THE thirty-fifth Clinical Congress of the American College of Surgeons will be host to the sixth Inter-American Congress of Surgery when it convenes in Chicago on October 21, 22, and 23. On its first day it will overlap with the Clinical Congress. The delegates and visitors from Latin American countries will be welcome to attend all sessions of the Clinical Congress, and the operative clinics at the hospitals.

The American College of Surgeons joined the Association of Inter-American Congresses of Surgery by vote of the Board of Regents on June 27, 1944.

This action was preceded by an invitation from Dr. Luis Vargas Salcedo of Santiago, Chile, dated July 21, 1942, to send two delegates as guests of honor to the first Inter-American Congress of Surgery in Santiago, held November 14 to 19, 1942. Dr. Leo Eloesser attended as delegate, and it was upon his enthusiastic recommendation that the College accepted the invitation to join. He also attended the second Congress held in Buenos Aires, October 10 to 15, 1943. Dr. Alton Ochsner was delegate to the third Congress, held in Rio de Janeiro from September 6 to 15, 1947. The fifth Congress was held in La Paz, Bolivia, October 17 to 21, 1948, with Dr. E. Payne Palmer of Phoenix and Dr. Hu Crim Myers of Philippi, West Virginia, as delegates and co-relators.

The surgical societies of the following countries, in addition to the United States, are members of the Association of Inter-American Congresses of Surgery: Argentina, Brazil, Bolivia, Chile, Cuba, Ecuador, Mexico, Panama, Paraguay, Peru, and Uruguay. Dr. Arnaldo Caviglia of Buenos Aires is the Secretary-General.

A preliminary outline of the program for the Sixth Inter-American Congress of Surgery follows:

Friday morning, October 21

Inaugural Ceremony

Friday afternoon, October 21

Delegates may attend the specialty panels of the Clinical Congress

Saturday morning, October 22

Main Theme: Acute Craniocerebral Trauma
Relator: E. Jefferson Browder, M.D., F.A.C.S., Brooklyn
Co-relators: To be appointed by each country

Saturday afternoon, October 22

Main Theme: Treatment of Injuries in the Region of the Ankle with Complications and Sequelae
Relator: Harrison L. McLaughlin, M.D., F.A.C.S., New York
Co-relators: To be appointed by each country

Saturday evening, October 22

Official Banquet

Sunday morning, October 23

Business Session

Sunday afternoon, October 23

Main Theme: Pulmonary Carcinoma
Relator: Evarts A. Graham, M.D., F.A.C.S., St. Louis
Co-relators: To be appointed by each country